The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 139, NO. 12 — CHICAGO, ILLINOIS — MARCH 19, 1949

COPYRIGHT, 1949, BY AMERICAN MEDICAL ASSOCIATION

SPECIFIC THERAPY OF BACTERIAL INFECTIONS OF CENTRAL NERVOUS SYSTEM

HARRY F. DOWLING, M.D.
LEWIS K. SWEET, M.D.
HAROLD L. HIRSH, M.D.
and
MARK H. LEPPER, M.D.
Washington, D. C.

Therapeutic agents are now available to combat most bacterial infections of the central nervous system. Consequently, proper treatment depends on (1) prompt diagnosis of the disease, (2) prompt determination of the etiologic agent and (3) selection of the appropriate drug or antibiotic. Since such selection depends on the causative organism in any given case, we have arranged the present discussion according to the bacteria responsible for the various diseases.

MENINGITIS CAUSED BY GRAM-NEGATIVE COCCI

Meningococcic Meningitis.—Meningococcic meningitis is the most frequent type of meningitis. Excellent results have been obtained with sulfadiazine or sulfamerazine. The dose for adults is 6 Gm. immediately and 1 Gm. every four hours and for children 70 mg. per kilogram (½ grain per pound) of body weight immediately and 150 mg. per kilogram (1 grain per pound) for each twenty-four hours thereafter, at four hour intervals. Comatose patients should be given an initial intravenous dose of 0.5 per cent solution of the sodium salt in sixth-molar lactate or isotonic sodium chloride solution. Subsequent doses are preferably given by stomach tube or by mouth, since this insures more constant blood levels, although the subcutaneous route may be used instead. Sodium bicarbonate, 6 Gm. at the start and 3 Gm. every four hours, should be used concomitantly in order to minimize the possibility of the formation of renal calculi. We [1] have recently obtained successful results in a few patients with meningococcic meningitis by the use of Nu-445,[2] a sulfonamide drug which is very soluble and has not yet been observed to cause renal calculi. Many more patients will have to be treated, particularly during an epidemic, before it will be possible to say that this drug is as good as sulfadiazine or sulfamerazine.

We have not found it necessary to employ penicillin routinely in meningococcic meningitis except in patients with a fulminating infection (the Waterhouse-Friderichsen syndrome). It is also used in patients who do not respond to sulfonamide drugs within twenty-four to forty-eight hours. Probably the most satisfactory way to administer penicillin for these purposes is in doses of 1,000,000 units intramuscularly every two hours, as will be shown in the discussion on pneumococcic meningitis.

The effects of therapy may be judged by (1) the rapidity of the fall in temperature and decrease in toxicity, (2) the disappearance of the meningococci from the cerebrospinal fluid and the increase in its dextrose content and (3) the decrease in the leukocyte count of the cerebrospinal fluid. Treatment with sulfonamide compounds and penicillin may be discontinued one week after the temperature drops if the patient is doing well in all other respects. The results which we have obtained [3] with this regimen are given in table 1. It will be seen that the fatality rate for all cases was 8.8 per cent and that it increased progressively with age. The fatality rate for comatose patients was double that for the entire series.

Gonococcic Meningitis.—Gonococcic meningitis is a much rarer condition. We have observed only 2 patients since the sulfonamide compounds have been available. Both recovered promptly under sulfonamide therapy. We recommend the same treatment as for the meningococcic type.

MENINGITIS CAUSED BY GRAM-POSITIVE COCCI

Pneumococcic Meningitis.—Pneumococcic meningitis is the most frequently observed disease in this group. The orthodox method of treatment consists of daily intrathecal injections of 10,000 to 20,000 units of penicillin plus sulfonamide drugs and 500,000 to 2,000,000 units of penicillin systemically. Intrathecal administration of penicillin has been considered necessary because many investigators have found that when penicillin is administered systemically, diffusion into the cerebrospinal fluid is irregular or does not occur.

Previous studies in our laboratory [4] have shown that several factors are important in obtaining and maintaining a satisfactory concentration of penicillin in the cerebrospinal fluid: (1) sufficiently large amounts of penicillin must be administered systemically; (2) the penicillin must be given for a certain interval before it appears in the cerebrospinal fluid, and (3) penicillin diffuses into the cerebrospinal fluid more freely in the presence of inflammation. Schwemlein and his co-workers [5] reported that detectable concentrations of penicillin were present in the spinal fluid of patients who received

Read before the Section on Nervous and Mental Diseases at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

From the George Washington University and Georgetown University Medical Divisions and the Contagious Disease Service, Gallinger Municipal Hospital and the Departments of Medicine and Pediatrics, George Washington and Georgetown Universities.

1. Brickhouse, R. L.; Lepper, M. H., and Dowling, H. F.: Treatment of Various Infections with Nu-445, Am. J. M. Sc., to be published.
2. Supplied by Hoffmann-LaRoche, Inc.
3. Zeller, W. W.; Hirsh, H. L.; Sweet, L. K., and Dowling, H. F.: Treatment of Meningitis with Sulfadiazine and Sulfamerazine, J. A. M. A. **136:** 8-12 (Jan. 3) 1948. Sweet, L. K.; Dumoff-Stanley, E., and Dowling, H. F.: Meningococcic Meningitis Treated with Sulfadiazine and Sulfamerazine: A Three-Year Study, Ann. Int. Med. **23:** 338-348 (Sept.) 1945. Lepper, M. H.; Sweet, L. K., and Dowling, H. F.: The Treatment of Meningococcic Infections with Sulfadiazine and Sulfamerazine (Sulfamethyldiazine, Monomethylsulfadiazine), J. A. M. A. **123:** 134-138 (Sept. 18) 1943.
4. Dumoff-Stanley, E.; Dowling, H. F., and Sweet, L. K.: The Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid, J. Clin Investigation **25:** 87-93 (Jan.) 1946.
5. Schwemlein, G. X.; Barton, R. L.; Bauer, T. J.; Loewe, L.; Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. **130:** 340-341 (Feb. 9) 1946.

20,000,000 units or more of penicillin during the course of twenty-four hours by continuous intravenous injection. We [6] gave 1,000,000 units intramuscularly at two hour intervals to 13 patients with and without meningitis and found that small amounts of penicillin were present in all patients within the first two hours after the first injection. After eight hours the spinal fluid concentrations in the patients with meningitis were

TABLE 1.—*Results of the Treatment of Meningococcic Meningitis with Sulfonamide Drugs*

	All Patients			Patients Admitted in Coma		
		Died			Died	
Age	No. Treated	No.	Per Cent	No. Treated	No.	Per Cent
0-9	47	1	2.1	14	1	7.1
10-19	52	3	5.8	26	2	7.7
20-29	66	5	7.6	28	5	17.9
30-39	65	3	4.6	26	3	11.5
40-49	28	5	17.9	19	5	26.3
50-59	20	6	30.0	15	6	40.0
60 +	17	3	17.6	11	3	27.3
Total	295	26	8.8	139	25	18.0

between 0.08 and 2.5 units per cubic centimeter. We [6] have treated 22 patients with pneumococcic meningitis with doses of 1,000,000 units every two hours. Three patients also received a single intrathecal injection of penicillin and 12 received sulfonamide compounds. Eight patients died of meningitis, giving a case fatality rate of 36 per cent. This compares favorably with a fatality rate of 62 per cent among the 66 patients previously treated by us with smaller doses of penicillin systemically plus repeated intrathecal injections of penicillin. We therefore advocate as the best treatment for pneumococcic meningitis available today 1,000,000 units of penicillin intramuscularly every two hours. Patients in coma or in extremis when treatment is begun may be given a single initial intrathecal dose of penicillin in addition. Sulfonamide compounds do not appear to be necessary when these doses are used.

Meningitis Caused by Staphylococci and Beta Streptococci.—Meningitis caused by these organisms is usually treated by multiple intrathecal injections plus systemic doses of penicillin. We have successfully treated 1 patient with meningitis caused by beta hemolytic streptococci with systemic doses of 1,000,000 units of penicillin every two hours and without intrathecal therapy. We have not had an opportunity to treat any patients with staphylococcic meningitis in this manner, but believe that this treatment should be as successful as in pneumococcic meningitis.

MENINGITIS CAUSED BY GRAM-NEGATIVE RODS

Hemophilus Influenzae Meningitis.—This type of meningitis responds well to streptomycin. Infants and young children may be given 1.5 Gm. per day, divided into 4 six hour intramuscular doses. Adults should receive 3 Gm. per day. Daily intrathecal injections of 25 mg. are also given to young children and 50 mg. to older children and adults.

Although streptomycin is usually successful when given alone, we believe that sulfadiazine should be given at the same time because of its effect on H. influenzae, because it may help to prevent the appearance of streptomycin-fast organisms and because it will inhibit the multiplication of gram-positive organisms during streptomycin therapy. The doses should be the same as in meningococcic meningitis.

When treatment is delayed or the patient is critically ill when therapy is started, or if no improvement occurs after forty-eight hours of streptomycin-sulfadiazine therapy, specific rabbit antiserum should be given in doses of 100 to 200 mg. of antibody nitrogen. About 90 per cent of patients will recover when they are treated in this manner.

Meningitis Caused by Other Gram-Negative Rods.—Meningitis caused by other gram-negative rods, such as Escherichia coli, Pseudomonas aeruginosa (pyocyaneus), Klebsiella pneumonia (Friedländer's bacillus) and Aerobacter aerogenes should be treated in the same way as H. influenzae meningitis, except that specific serum would not be used. Since these types of meningitis are often an end stage of an overwhelming infection, the prognosis is uncertain and often depends on factors other than the meningitis itself.

TUBERCULOUS MENINGITIS

The early results with streptomycin in this disease appeared to be excellent. Clinical arrest occurs in one fourth of the patients. The results are especially favorable in patients who had meningitis without miliary tuberculosis. Not all of the patients with arrested disease recover, however. The longer they are followed the higher becomes the percentage of relapses, until now it seems likely that no more than 5 or 10 per cent of patients with tuberculous meningitis will recover completely and most of these will have some permanent neurologic damage. A ray of hope is offered by the results of Lincoln and her associates.[7] They obtained

TABLE 2.—*Suggested Treatment for Various Types of Bacterial Meningitis*

Etiology	Sulfonamide Drug	Penicillin	Streptomycin
Gram-neg. cocci Meningococci Gonococci	Sulfadiazine or sulfamerazine systemically	In fulminating infections as for gram-pos. cocci	None
Gram-pos. cocci Pneumococci Beta streptococci Staphylococci	None	1,000,000 units intramuscularly every 2 hours; in comatose patients initial intrathecal injection of 20,000 units	None
Gram-neg. rods H. influenzae * E. coli Ps. aeruginosa and others	Sulfadiazine or sulfamerazine systemically	None	Systemically, 3 Gm./day to adults; 1.5 Gm./day to infants; intrathecally 50 mg./day to adults and 25 mg./day to young children
Tubercle bacillus	None	None	Systemically, 9 mg./Kg./day (maximum 2 Gm.); intrathecally, 1 mg./Kg. (maximum 50 mg.)/day; then on alternate days

* In cases of severe disease, specific serum in doses of 100 to 200 mg. of antibody nitrogen.

clinical arrest in 6 of 7 patients treated with a combination of streptomycin and promizole* (4,2′-diaminophenyl-5′-thiazolyl sulfone). Prolonged follow-up on these patients as well as further studies on combinations of streptomycin and various antituberculous chemicals will be welcome.

Patients with tuberculous meningitis should be treated as early in the course of the disease as possible with

6. Dowling, H. F.; Sweet, L. K.; Robinson, J. A.; Zeller, W. W., and Hirsh, H. L.: The Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin, Am. J. M. Sc., to be published.

7. Lincoln, E. M.; Kirmse, T. W., and DeVito, E.: Tuberculous Meningitis in Children: A Preliminary Report of Its Treatment with Streptomycin and "Promizole," J. A. M. A. **136**:593-597 (Feb. 28) 1948.

intramuscular doses of 9 mg. per kilogram of body weight per day, up to a maximum of 2 Gm., at six hour intervals. Intrathecal doses of 1 mg. per kilogram, up to a maximum of 50 mg., are also given, at first at daily intervals and after two weeks on alternate days. It is usually recommended that treatment be continued for four months, but it is doubtful whether streptomycin is of any value after six to eight weeks. The spinal fluid leukocyte count and protein content are no criteria of recovery. More reliable are the absence of organisms in smear and culture and a return of dextrose content to normal.

LOCALIZED INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

The same procedures should be used in the treatment of abscesses as are used in meningitis. The causative organism should be determined and the proper antibiotic or sulfonamide compound should be used. Surgical drainage with local instillation of the proper antibiotic should be employed where advisable.

SUMMARY

The treatment advocated in the various types of meningitis caused by bacteria is outlined in table 2. Meningitis caused by gram-negative cocci is best treated with sulfonamide compounds, penicillin being used as an adjuvant in cases of severe disease. When gram-positive cocci are the cause, penicillin should be given in massive doses systemically. Comatose patients may receive one intrathecal dose at the start of treatment. In meningitis caused by gram-negative rods, sulfonamide compounds should be given in combination with streptomycin. In severe H. influenzae infections, specific serum should be given also. In tuberculous meningitis, systemic and intrathecal administration of streptomycin should be continued for several weeks or months.

139
49

ABSTRACT OF DISCUSSION

DR. PAUL S. RHOADS, Chicago: Dr. Dowling emphasizes two procedures which I am sure are not in general use. One is the administration of maintenance doses of sulfonamide drugs in comatose patients by stomach tube after an initial 6.0 Gm. dose of the sodium salt intravenously. I am sure the method accomplishes what he is after—the avoidance of fluctuations in the blood level. Since comatose patients require almost constant administration of fluids intravenously we usually continue the maintenance dose by adding 1.0 Gm. of sodium sulfadiazine to them every four hours or 2.0 Gm. of sodium sulfamerazine every eight hours—and have found that fluctuations in blood level on this schedule are not violent. He spoke of the use of a new sulfonamide drug prepared by the Hoffman-LaRoche Company which is more soluble in the urine than the ones now in general use, and which is not irritating when given intramuscularly as the lithium salt. We have used this drug as the sole antibacterial therapy in 8 cases of meningococcic meningitis and in combination with penicillin in 3 others—and all the patients recovered. Probably when this or other sulfonamide drugs which can safely be injected into the muscle in 20 to 40 per cent solution come into general use the need for administration by stomach tube will be over. The other new departure emphasized by Dr. Dowling is the intramuscular injection of 1,000,000 units of penicillin every two hours in pneumococcic meningitis and certain other severe infections of the central nervous system. By this technic he is able to produce an effective level of penicillin in the spinal fluid in most cases. The results—even without the combined use of sulfonamide compounds—compare favorably with those in any large series of patients with pneumococcus meningitis yet reported. Whether the advantages of this method—which is expensive and requires twelve intramuscular injections each twenty-four hours—outweigh the possible danger of a single intrathecal injection of 10,000 to 20,000 units of penicillin each twenty-four hours I am not prepared to say. In our experience there have been no difficulties with intrathecal administration in this dosage, and we have always found a satisfactory level of penicillin in the spinal fluid twenty-four hours later. I am not quite ready to abandon daily intrathecal injections in patients with a poor prognosis in favor of this method, although I am heartily in favor of larger parenteral penicillin dosage than we have used in the past. In the treatment of meningitis due to H. influenzae I agree that streptomycin is probably the single most effective agent.

DR. WESLEY W. SPINK, Minneapolis: In the face of standardized recommendations for treating pneumococcic meningitis, Dr. Dowling and his co-workers are to be commended for withholding the intrathecal injection of penicillin in a significant group of patients. They have shown that the parenteral administration of large doses of penicillin will result in the drug's penetrating the blood-brain barrier and appearing in sizable quantities in the cerebrospinal fluid. This applies to the patient with inflamed meninges, but not to normal persons. I agree with Dr. Dowling that sulfadiazine or sulfamerazine is the drug of choice in the treatment of meningococcic meningitis and that in this infection intrathecal therapy is not necessary. Our group has been interested in the problem as to whether it is mandatory that solutions of penicillin be administered intrathecally for pneumococcic meningitis, as well as being given parenterally. We have not been particularly concerned about the harmful effects of intrathecally administered penicillin, and have observed no undesirable reactions following this procedure. Perhaps this is due to the fact that no more than 20,000 units of penicillin have been injected in 10 cc. of isotonic sodium chloride solution. Until the present time, we have insisted on the intrathecal administration of penicillin as a part of the routine treatment of pneumococcic and staphylococcic meningitis. Recent investigations in our laboratory tend to confirm the conclusion of Dr. Dowling that large amounts of parenterally administered penicillin will result in good concentrations of the antibiotic in the cerebrospinal fluid. In accordance with the suggestion of King and his group at Mount Sinai Hospital in New York, 1,000,000 units of the crystalline sodium salt of penicillin G in 5 cc. of distilled water has been rapidly injected intravenously into each of several human subjects. This procedure will result in blood levels of over 100 units per cubic centimeter. Thirty minutes later one-half this amount is present. In persons with normal meninges, the concentration of penicillin in the cerebrospinal fluid did not exceed 0.5 unit per cubic centimeter at any time, whereas in patients having inflamed meninges, levels up to 8 units per cubic centimeter were attained in the cerebrospinal fluid. Such concentrations would appear to be adequate for eradicating pneumococci from the fluid. Most clinicians are now agreed that in the treatment of tuberculous meningitis streptomycin should be injected into the subarachnoid space as well as administered intramuscularly. There is considerable doubt as to whether it is advisable to introduce more than 25 mg. of streptomycin at any one time, since amounts greater than this have provoked irritation of the meninges.

DR. WILLIAM P. BOGER, Philadelphia: Dr. Spink indicates that he has confirmed the passage of penicillin into the cerebrospinal fluid, but made the remark that it is difficult to pass a normal blood brain barrier. Recently, we reexamined this point and found that significant amounts of penicillin are found in the cerebrospinal fluid in the majority of normal patients, if 100,000 units of penicillin are administered intramuscularly at three hour intervals. Having demonstrated that in 20 of 25 patients this was true, the rapidity of passage of penicillin into the cerebrospinal fluid was studied. We were able to demonstrate that a single intravenous injection of 500,000 units of penicillin resulted in the appearance of penicillin in the spinal fluid within two hours. The amounts of penicillin in the cerebrospinal fluid were doubled when carinamide was administered intravenously with the same dose of penicillin, and when penicillin and carinamide were given together no case failed to show penicillin in the spinal fluid. This was a controlled series of cases, the same patients being

studied with penicillin alone and then later when penicillin was given in conjunction with carinamide. These findings were applied to the treatment of purulent meningitis. Within two hours following a single intravenous dose of 500,000 units of penicillin as much as 2 and 8 whole units of penicillin per cubic centimeter of cerebrospinal fluid have been observed. Since the samples were taken from the lumbar region it is implied from what is known of the formation of cerebrospinal fluid that within two hours penicillin had diffused throughout the subarachnoid space. Certainly, whole units of penicillin are bactericidal for pneumococci and, although we may be inclined to administer the antibiotic intrathecally, it would appear unnecessary in view of these findings.

DR. W. JAMES GARDNER, Cleveland: It is not unfortunate, but it is a fact that the appearance of penicillin on the medical horizon somewhat discouraged the further investigation of the effectiveness of the sulfonamide compounds. A fact which Dr. Dowling did not mention is that it has been found by laboratory work that the administration of urea enhances tremendously the effectiveness of the sulfonamide compounds. That is in vitro as well as in vivo, locally as well as systemically. The action of urea, and the method by which urea enhances the effectiveness of the sulfonamide compounds, is that it inhibits the normal inhibitors of sulfonamide compounds, and increases the solubility of the sulfonamides. It increases their ability to penetrate tissues and it may lower the blood brain barrier to the passage of sulfonamide compounds.

DR. PERCIVAL BAILEY, Chicago: After these infections have been cured, the rest of humanity that are left are gravitating to the hands of the neurologist. In my experience, I have seen several cases in which I have been convinced that intrathecal therapy increased these disabilities. I was therefore greatly pleased when Dr. Dowling stated that he no longer needed to put penicillin into the spinal fluid. I look forward to the day when he will cease putting streptomycin into the spinal column also. I have never believed that treatment was helped by putting the drug into the spinal canal.

DR. HARRY F. DOWLING, Washington, D. C.: With regard to Dr. Spink's findings on the penetration into the cerebrospinal fluid, we also found that in normal patients the penetration is not as good as in those with meningitis, but with the dose that we use we always obtain in a significant concentration after eight hours. We used this dose in a large enough series of patients to prove statistically that we had a method of treatment which was worth while. It is true, as Dr. Spink says, that when no more than 20,000 units is given at one time, we seldom get any neurologic complications, but there are cases reported in the literature in which these have occurred on a dose of 20,000 units. Not only that, I wish I could have had time to show you the rapid drop in temperature which occurred in the recovered patients who received this systemic penicillin as compared with those patients who received the combination. Also, pleocytosis disappeared much more rapidly in the recovered patients who received the systemic penicillin alone, as compared with those who received the combination. I think Dr. Spink has a point that we do not know yet what to recommend in staphylococcic meningitis. It is probably best to use the orthodox treatment of combined injections until we can prove that intrathecal injections are not needed. I was very interested in Dr. Gardner's remarks on urea. I feel that that is something worth investigating. We have not used it clinically. Dr. Boger's discussion pointed up the one fact that if we use some other method, particularly in his case carinamide, we may be able to get the same results that we got with our dose. We did not employ carinamide, although that seemed a feasible thing to do, because, as I say, we wanted to get enough patients who had been treated in exactly the same way to prove whether this method was worth while. I think in the future we will try some method similar to that mentioned by Dr. Boger. With regard to Dr. Bailey's statement on the use of streptomycin intrathecally, I know that there is a point. I wish I felt free to do without it, but the experience of the medical research council of England seems to show that it is necessary to use streptomycin intrathecally. Here we cannot raise the systemic dose, ad libitum, as we can with penicillin, in order to get penetration.

DANGER OF DICUMAROL® TREATMENT IN PREGNANCY

ALFRED P. KRAUS, M.D.
SAMUEL PERLOW, M.D.
and
KARL SINGER, M.D.
Chicago

The increasing use of dicumarol® in the prevention and treatment of thromboembolic phenomena brings up the clinically significant question whether this drug, when given to a pregnant woman, has any deleterious effects on the growth and development of the fetus. Schofield [1] in 1924 noticed that newborn calves appeared to be much more sensitive to toxic sweet clover hay than mature animals did. Roderick and Schalk [2] recorded similar experiences. Quick [3] gave dicumarol® to 2 dogs during their last week of pregnancy; he observed that the prothrombin levels of the newborn pups were definitely reduced (less than 1 per cent of normal), in spite of the fact that the prothrombin levels of the mothers were maintained well within a "safe" range. The pups also showed a decided tendency toward bleeding, and none of them survived, unless vitamin K was given. Quick concluded that the administration of dicumarol® is contraindicated during pregnancy. Our investigation was undertaken to observe the influence of dicumarol® not only on the newborn but also on the intrauterine growth and development of the fetus. The rabbit was selected for these experiments because of its short gestation period.

MATERIAL AND METHODS

Female rabbits weighing 3 to 6 Kg. were used in the experiments. The animals were kept in separate cages and fed only purina® rabbit chow and water. Determinations of the prothrombin time were performed by Quick's one stage method. It was realized that this test does not measure the true level of prothrombin alone but also indicates the interdependent actions of several components involved in the clotting process, namely, prothrombin, the fifth factor [4] (Ac-globulin [5] and labile factor [6]), thromboplastin and calcium, when, of course, a sufficient quantity of fibrinogen is present. The one stage method was selected because of its widespread clinical use, thus enhancing the interpretation of the experimental findings. For this reason also, the lower limit of the "safe" range was arbitrarily set at 10 per cent of normal, as it is commonly done in the dicumarol® therapy of human beings.[7]

Batches of thromboplastin were prepared from several rabbit brains according to Quick's acetone dehydration method.[8] A saline suspension was then made immediately, kept at 50 C. for fifteen minutes with constant stirring, centrifuged slowly for five minutes and stored in the dry ice box in stoppered vials

From the Department of Hematologic Research, Medical Research Institute, and the Department of Surgery, Michael Reese Hospital.

The Department of Hematologic Research is supported in part by the Michael Reese Research Foundation and the Hematology Research Foundation.

1. Schofield, F. W.: Damaged Sweet Clover: The Cause of a New Disease in Cattle Simulating Hemorrhagic Septicemia and Blackleg, J. Am. Vet. M. A. **64**: 553, 1924.
2. Roderick, L. M., and Schalk, A. F.: Studies on Sweet Clover Disease, Bulletin 250, North Dakota Agricultural Experiment Station, 1931.
3. Quick, A. J.: Experimentally Induced Changes in the Prothrombin Level of the Blood, J. Biol. Chem. **164**: 371, 1946.
4. Owren, P. A.: The Coagulation of the Blood, Oslo, J. C. Gundersen, 1947.
5. Ware, A. G.; Fahey, J. L., and Seegers, W. H.: Platelet Extracts. Fibrin Formation and Interaction of Purified Prothrombin and Thromboplastin, Am. J. Physiol. **154**: 140, 1948.
6. Quick, A. J.: A Modern Concept of the Coagulation of Blood, Marquette M. Rev. **13**: 89, 1948.
7. (a) Neuhof, H.: Venous Thrombosis, New York, Grune & Stratton, Inc., 1948, p. 36. (b) Allen, E. V.; Hines, E. A., Jr.; Kvale, W. F., and Nelson, W. B.: Use of Dicumarol as an Anticoagulant, Ann. Int. Med. **27**: 371, 1947. (c) Davidson, C. S., and MacDonald, H.: A Critical Study of Action of 3-3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**: 24, 1943.
8. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 312.

in aliquots of 1.5 cc.[9] Such a batch of thromboplastin retained its full potency for months and allowed direct comparison of the prothrombin times from day to day. Frequent prothrombin determinations on normal rabbits consistently gave values between six and seven seconds. Proper dilution curves were also performed at frequent intervals.

Blood for the prothrombin time determinations was drawn by means of heart puncture in the control animals and by ear vein puncture in dicumarolized animals. The ear vein puncture was used in preference to the heart puncture because of the danger of fatal hematopericardium in dicumarolized animals.[10] The blood of the newborn rabbits was drawn by heart puncture. The babies usually did not survive the heart puncture for more than one day. Therefore, the prothrombin time was not determined in all the litter mates, but in a representative group only, in order to permit the study of survival rate of the newborn rabbits.

Dicumarolization was accomplished by placing the appropriate quantity of pure dicumarol® powder [11] into no. 5 gelatin capsules. These capsules were put into one end of a short piece of rubber tubing. The rabbit's mouth was held open by a gag, the tube inserted deeply into the pharynx and the capsules flushed out of the tube with 2 to 3 cc. of water by means of a syringe.[12] This procedure prevented the regurgitation of the capsule. Although the oral application of dicumarol® introduces the conceivable factor of variable absorption into the experimental conditions, we found that this type of administration gave satisfactory results. The oral route also seemed preferable because it was thought that daily injections into the ear veins might increase the danger of undesirable damage to these vessels, which were already so often used for obtaining blood for the prothrombin determinations. Intraperitoneal administration seemed inadvisable because of the possible interference with the pregnant state of the animals.

Prothrombin Times of Pregnant Rabbits Receiving No Dicumarol®

	Prothrombin Times							
	1		2		3		4	
Animal	Sec.	%	Sec.	%	Sec.	%	Sec.	%
Mother	6.4	100	7.0	100	7.0	100	6.4	100
Baby 1	7.0	75	7.4	87	8.0	60	6.4	100
Baby 2	7.0	75	7.4	85	8.6	45	6.4	100
Baby 3	...	...	...	...	8.6	45	6.6	95

RESULTS

I. *Controls.*—Four pregnant rabbits were used as controls and did not receive any dicumarol.® The results are compiled in the table.

The somewhat lower prothrombin levels demonstrated in the babies of mothers no. 1 and no. 2 and the even more depressed levels of the babies of mother no. 3 might be explained by the drop of prothrombin value in newborn rabbits during the first twenty-four hours as determined with the one stage method.[8] This phenomenon has been described by numerous investigators.[13] These babies were born during the night, and the determinations of the prothrombin time were not performed until the next morning, corresponding to an interval of eight to twelve hours. The babies of rabbit no. 4 were examined within one hour after birth and consequently showed practically normal prothrombin values.

II. *Effect of "Unsafe" Doses of Dicumarol.®*—Four rabbits received doses of dicumarol® sufficient to cause depression of the prothrombin level to less than 10 per cent of normal. These low levels were never maintained for more than a few days. Whenever the prothrombin level reached such low values, the drug was withheld. However, no vitamin K was given at any time.

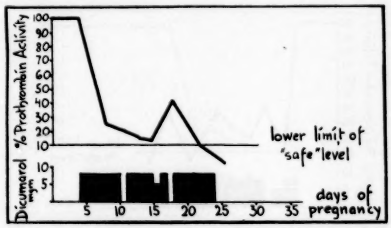


Fig. 1.—Graph showing effect of "unsafe" doses of dicumarol® on prothrombin levels of rabbit no. 5. Seven macerated fetuses were found in utero, weighing 17 to 21.5 Gm., which had been dead for at least several days prior to the death of the mother.

Rabbit no. 5 was started on 8 mg. of dicumarol® on the fifth day of pregnancy. The prothrombin level fell to 25 per cent by the eighth day and thereafter was maintained between 10 and 25 per cent, with the exception of the eighteenth day, when it rose to 40 per cent. On a continued daily dose of 8 mg. of dicumarol,® the prothrombin level fell to less than 1 per cent on the twenty-fifth day; the rabbit died on the twenty-sixth day, two days after discontinuation of the dicumarol® administration. Blood was observed in the nostrils and vaginal bleeding had started. Postmortem examination disclosed multiple hemorrhages into the lungs. The uterus contained about 100 cc. of nonclotted blood. In the uterus were found seven baby rabbits, weighing between 17.0 and 21.5 Gm., as compared with normal weights of 30 to 60 Gm. All fetuses were macerated and showed evidence of having been dead several days prior to the death of the mother.

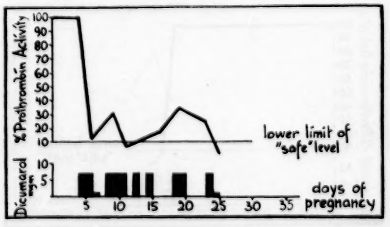


Fig. 2.—Graph showing effect of "unsafe" doses of dicumarol® on prothrombin levels of rabbit no. 6. One baby (weight, 25 Gm.) was born dead. Eight macerated fetuses, weighing 10 to 40 Gm., were found in utero.

Rabbit no. 6 was started on 7 mg. of dicumarol® on the fifth day of pregnancy. By the sixth day the prothrombin level had fallen to 12 per cent of normal. Only 1 mg. of dicumarol® was given on that day and the drug was withheld the next day. By the ninth

9. Fuller, J.: Frozen Thromboplastin Extracts in Prothrombin Determinations, Am. J. Clin. Path. **17:** 891, 1947.
10. Quick, A. J.: Experimentally Induced Changes in the Prothrombin Level of the Blood, J. Biol. Chem. **161:** 33, 1945.
11. Dicumarol® powder was supplied by Abbott Laboratories, North Chicago, Ill.
12. Singer, K.: Experimentelle Beiträge zum Problem der Pathogenese der perniziösen Anämie: Ueber künstliche Infektion von Hunden mit Bothriocephalus latus, sowie über die Methoden zur tierexperimentellen Erzeugung einer Achylie, Ztschr. f. d. ges. exper. Med. **79:** 398, 1931.
13. Quick,[8] Brinkhous, K. M.: Plasma Prothrombin: Vitamin K, Medicine **19:** 329, 1940. Quick, A. J., and Grossman, A. M.: The Nature of the Hemorrhagic Disease of the Newborn, Am. J. M. Sc. **199:** 1, 1940. Waddell, W. W., Jr., and Lawson, G. M.: Hemorrhagic Diathesis of the Newborn: Further Observations Concerning Prevention and Treatment, J. A. M. A. **115:** 1416 (Oct. 26) 1940.

day a prothrombin level of 30 per cent was found. On the eleventh day the prothrombin level again had fallen to only 6 per cent of normal. Thereafter, prothrombin was kept above 10 per cent, at one time reaching 35 per cent. However, on the twenty-fifth day a dangerously low level was present (2 per cent). Dicumarol®

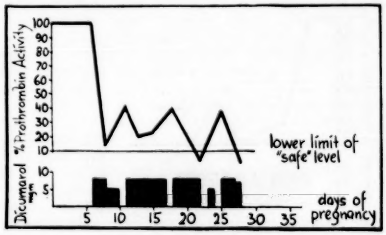


Fig. 3.—Graph showing effect of "unsafe" doses of dicumarol® on prothrombin levels of rabbit no. 7. Four babies (weight, 30 to 44.5 Gm.) were born dead; 2 fetuses were found in utero (weight, 1 and 36.5 Gm., respectively). All showed severe maceration.

was again discontinued, and the rabbit died on the twenty-ninth day, after delivering one dead fetus weighing 25 Gm. There was considerable blood in the cage. On postmortem examination the uterus contained about 40 cc. of liquid and some clotted blood. Eight infant rabbits were found in utero. Two of these were very small, weighing only 10 and 12 Gm., respectively, and consisting mainly of placental tissue with some unrecognizable tissue attached to it. The other 6 babies weighed between 30 and 40 Gm. and were relatively well developed. From the discrepancy in weight and development of the infant rabbits, it may be surmised that the two immature ones died during the first episode of dicumarol® poisoning on about the eleventh day of pregnancy, while the remainder survived until about the twenty-fourth day of pregnancy.

Rabbit no. 7 was started on 8 mg. of dicumarol® on the sixth day of pregnancy. It was maintained on prothrombin levels between 10 and 40 per cent of normal until the twenty-second day of pregnancy, when an "unsafe" level of 3 per cent was reached.

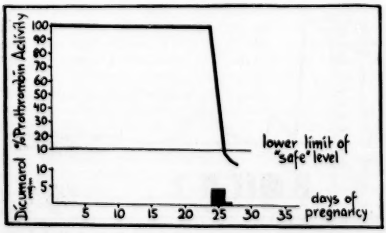


Fig. 4.—Graph showing effect of "unsafe" doses of dicumarol® on prothrombin levels of rabbit no. 8. Two babies were born dead and 7 alive (weight, 40 to 60 Gm.).

Dicumarol® was discontinued for one day; the next day only 5 mg. was given, and the day after, dicumarol® again was omitted. On resumption of administration of the drug, the prothrombin level again dropped to 1 per cent on the twenty-eighth day, and the rabbit died on the thirtieth day, after delivering four dead babies weighing between 30 and 44.5 Gm. The rabbit lost a considerable amount of blood during the delivery. Three of the four baby rabbits were macerated. On postmortem examination two infant rabbits were found in the uterus, one weighing 36.5 Gm. and one 1 Gm. The uterus contained 20 cc. of nonclotted blood and a blood clot measuring 2 by 10 cm. The rabbit also showed some retroperitoneal hemorrhage and bleeding into the wall of the colon.

Rabbit no. 8 was not started on dicumarol® until the twenty-fourth day of pregnancy. A total dose of only 10.5 mg. of dicumarol® was given. In spite of this small dose, the prothrombin level fell to 2 per cent of normal on the twenty-eighth day and the rabbit died on the thirty-first day, after delivering two dead and seven live babies. The prothrombin level of two of these infant rabbits was 37 per cent of normal immediately after birth. This was four days after dicumarol® had been discontinued in the mother.

These experiments demonstrate that none of the mother rabbits showing a fall of the prothrombin level below 10 per cent of normal at one time or another during pregnancy survived. None of the fetuses survived up to the time of delivery except those of rabbit no. 8, which received dicumarol® only during the last week of the gestation period. The fetuses were small, with conspicuous maceration of the skin and

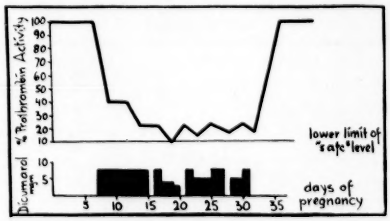


Fig. 5.—Graph showing effect of "safe" doses of dicumarol® on prothrombin level of rabbit no. 9. Two severely macerated babies (weight, 18 and 20 Gm., respectively) were born dead. Four were born alive (weight, 55 to 64 Gm.) with signs of hemorrhagic tendency.

decomposition of the tissues. These fetal changes resulted in spite of the fact that the "unsafe" levels of prothrombin (below 10 per cent) were not maintained for more than two to three days. There were no signs of manifest bleeding in the live babies, which after delivery showed normal development.

III. *Effect of "Safe" Levels of Dicumarol.®*—Four pregnant rabbits were kept at a "safe" level of dicumarol® administration during their gestation period.

Rabbit no. 9 was started on 8 mg. of dicumarol® per day on the seventh day of gestation. The prothrombin level fell to 40 per cent on the ninth day and to 22 per cent on the fourteenth day and thereafter was maintained between 10 and 25 per cent by means of 5 to 8 mg. of the drug for the remainder of the pregnancy. It delivered six babies on the thirty-first day of pregnancy. Two of these were born dead, weighing only 18 and 20 Gm., respectively. They were badly macerated, indicating early intrauterine death. Two infant rabbits died within thirty minutes after birth; they showed widespread hemorrhages and weighed 55 and 62 Gm., respectively. The fifth baby rabbit weighed 64 Gm., had a prothrombin level of 2 per cent (that of the mother was 18 per cent) and was bleeding from the nostrils. The last baby weighed

57 Gm. with a prothrombin level of 5 per cent of normal. Both these babies died within thirty-six hours.

Rabbit no. 10 was given 8 mg. of dicumarol® per day, starting on the sixth day of pregnancy. The prothrombin level showed considerable fluctuation, reaching 36 per cent on the fifteenth day, 90 per cent on the eighteenth day, 20 per cent on the twenty-eighth day, 50 per cent on the thirtieth day and, finally, 18 per cent on the day of delivery. Thirteen live baby rabbits were born on the thirty-second day of pregnancy. In a representative group of four infant rabbits, including the animals of the lowest and highest weight, two with and two without outward signs of hemorrhage, the prothrombin levels were all demonstrated to be below 1 per cent of normal. Two of the other babies also showed evidence of hemorrhage. Eight babies were dead one day after delivery, including the four who underwent heart puncture. All baby rabbits died within five days after delivery. The mother did not lose an excessive amount of blood during delivery and remained healthy.

Rabbit no. 11 was started on 8 mg. of dicumarol® on the seventeenth day of pregnancy. The prothrombin level reached 23 per cent on the twenty-first day and then remained between this level and 10 per cent up to the day of delivery. The rabbit gave birth to eleven

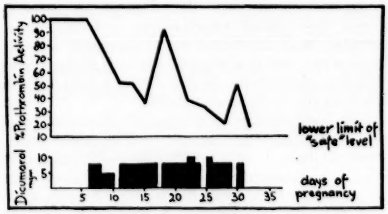


Fig. 6.—Graph showing effect of "safe" doses of dicumarol® on prothrombin levels of rabbit no. 10. Thirteen live babies (weight 24 to 55 Gm.) were born with signs of hemorrhagic tendency.

babies on the thirty-first day; one of them was born dead, weighed 33 Gm. and showed some signs of maceration. The prothrombin level in five of the live infant rabbits on the day of delivery was less than 1 per cent. One baby had a prothrombin level of 2 per cent. The day after delivery one baby rabbit had a prothrombin level of 18 per cent and another one of 25 per cent. The two infant rabbits which were not subjected to heart puncture died the day after delivery, and all babies were dead by the fifth day.

Rabbit no. 12 began to receive dicumarol® (7 mg. daily) on the fourth day of pregnancy. The prothrombin level fell to 50 per cent on the sixth day and to 40 per cent on the eleventh day. Then the level rose to 80 per cent on the sixteenth day and fell to 29 per cent on the nineteenth day. The animal started vaginal bleeding on the twenty-first day of pregnancy and passed some tissue and blood clots. No further dicumarol® was given; however, the rabbit died on the twenty-sixth day. The uterus contained eleven macerated, bady decomposed fetuses, measuring 1 to 3 cm. in length, and some bloody fluid. The uterine wall showed hemorrhagic areas. On microscopic examinations, placental tissue could be recognized with certainty; however, the fetuses themselves were too badly decomposed to allow recognition of any of the organs. No other abnormalities were observed in the mother.

These experiments show quite clearly the damaging effect of even "safe" doses of dicumarol® on the embryos. While 3 of the 4 mother rabbits survived after delivery and did not have any excessive intrapartum and postpartum bleeding, the babies sustained an extreme depression of their prothrombin levels at

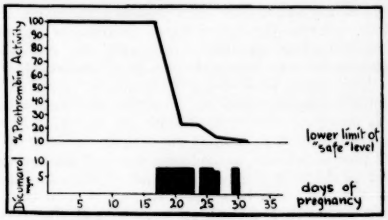


Fig. 7.—Graph showing effect of "safe" doses of dicumarol® on prothrombin levels of rabbit no. 11. One macerated baby was born dead (weight, 33 Gm.). Ten were born alive (weight, 34 to 51.5 Gm.) with signs of hemorrhagic tendency.

birth. The newborn rabbits exhibited a pronounced hemorrhagic tendency, and their longest survival time was five days. A few fetuses died before delivery.

COMMENT

The occurrence of thrombosis in pregnant women brought up the question of the advisability of dicumarol® therapy in this condition. A search through the literature did not reveal any experimental studies of this clinically significant problem, with the exception of the animal experiments by Quick.[3] Neuhof [7a] stated that dicumarol® is contraindicated during pregnancy and based this statement on the belief that the drug will cause excessive hemorrhage during and after delivery. Von Sydow [14] observed 1 patient who received the drug during the last month of pregnancy. The newborn infant showed severe subcutaneous hemorrhages, and treatment with vitamin K did not increase the prothrombin level until six days after birth.

Our experiments seem to demonstrate that dicumarol® passes the placental barrier. Three of the 4 animals kept on "safe" prothrombin levels during the

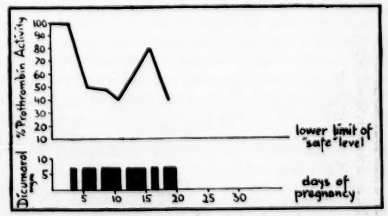


Fig. 8.—Graph showing effect of "safe" doses of dicumarol® on prothrombin levels of rabbit no. 12. Eleven macerated fetuses were found in utero.

administration of the drug delivered in a normal manner and showed no evidence of excessive intrapartum and postpartum bleeding. The fourth aborted on the twenty-first day and died five days later. However,

14. von Sydow, G.: Hypoprothrombinemia and Cerebral Injury in Infant After Dicumarol Treatment of Mother, Nord. med. **34**: 1171, 1947; abstracted in Videback, A.: A Review of the Scandinavian Literature on Hematology from the Years 1946 and 1947, Acta Haemat. **1**: 126, 1948.

in the babies of these rabbits an extreme depression of the prothrombin levels at birth was demonstrable, together with a definite hemorrhagic tendency. The longest survival time was five days. A few of the newborn rabbits died during one time or another of the gestation period. The drop of the prothrombin level in these infant rabbits was much more pronounced than in the mothers and was present immediately after birth, whereas the "physiologic" decrease of the prothrombin time, as determined with the one stage method, develops later and is never so remarkable.

When given toxic doses of dicumarol,® none of the mothers survived delivery. Intrapartum hemorrhage was observed consistently. With the exception of the babies of rabbit 8, none of the fetuses survived up to the time of delivery, as evidenced by small size, maceration of the skin and decomposition of organs. Rabbit no. 8 appeared to be a hyperreactor. A total dose of only 10.5 mg. of dicumarol® over a three day period resulted in a drop of the prothrombin level to 1 per cent of normal. Such exaggerated responses have been described previously in animals [10] and are not infrequently observed in human beings (20 to 25 per cent of those receiving the drug are hyperreactors).[15]

From the results of these experiments, dicumarol® appears to be a dangerous drug when given during pregnancy. It produces extremely low prothrombin values and, subsequently, serious hemorrhagic disease in the newborn. Prothrombin values below 10 per cent of normal cannot be avoided with certainty during dicumarol® treatment because of the unpredictable occurrence of a hyperreactive response, and furthermore because of the twenty-four to forty-eight hour lag in the effect of this drug; there is, therefore, always the danger of causing irreversible damage to the fetus and possibly intrauterine death. Our experiments demonstrate that a prothrombin level below 10 per cent for two days, and possibly even less time than that, may irreversibly injure the fetus.

While it is realized that results of animal experiments may not be directly applicable to human beings, the similar reactions of rabbits, dogs [3] and cattle [16] are strongly suggestive of similar processes in human beings.

SUMMARY

The effect of continuous dicumarol® administration on the intrauterine growth and development of the fetus was studied in pregnant rabbits. When given in doses which produced an "unsafe" level of prothrombin (below 10 per cent of normal) in the mother, even for not more than two days, the fetuses died in utero. They were small, showing conspicuous maceration of the skin and decomposition of the organ tissues. When "safe" prothrombin levels were maintained in the mother, the infant rabbits revealed an extreme decrease of their prothrombin at birth, with a definite hemorrhagic tendency. The mothers, however, did not experience excessive intrapartum or postpartum hemorrhage.

Dicumarol® affects the prothrombin level of the infant to a much greater extent than that of the mother. Although animal experiments may not be directly applicable to human beings, it would appear that dicumarol® treatment is not advisable in the pregnant woman, since it may seriously interfere with the normal development of the fetus or cause fetal death.

15. Cosgriff, S. W.; Cross, R. J., and Habif, D. V.: Excessive Hypoprothrombinemia Due to "Dicumarol": Its Treatment with Lyophilized Plasma, J. A. M. A. **138**: 405 (Oct. 9) 1948.

16. Schofield,[1] Roderick and Schalk.[2]

FATAL HEMORRHAGE IN DICUMAROL® POISONING

With Report of Necropsy

IVAN F. DUFF, M.D.
and
WILLIAM H. SHULL, M.D.
Ann Arbor, Mich.

The hazard of hemorrhagic diatheses resulting from the use of dicumarol® has been repeatedly emphasized, and considerable accumulated clinical experience has established definite contraindications to its prescription. As outlined by Barker [1] and Allen,[2] the conditions under which the drug should be used cautiously, if at all, include significant hepatic and renal insufficiency, ulcerative lesions of the gastrointestinal tract, purpura of any type, blood dyscrasias with a bleeding tendency and, particularly, thrombocytopenia, subacute bacterial endocarditis and after recent operations on the brain or spinal cord where even minor degrees of bleeding might be associated with grave consequences. To this list others [3] have added severe hypertension, recent threatened abortions and obstetric cases near term. Lack of adequate and reliable laboratory facilities for the daily measurement of prothrombin activity must be regarded as the most important of all contraindications. The official Swedish civil and army medical committee have concluded that dicumarol® should be administered only in a hospital where facilities exist for estimating prothrombin time and have issued a warning against its use in general practice.[4]

There have been several reports [5] of severe hemorrhage associated with the use of dicumarol® since it became available in 1941, and the number of unreported cases is increasing.[6] Bleeding has sometimes been difficult to control despite the use of adequate quantities of vitamin K and blood transfusions.

Reports of 21 deaths attributed to dicumarol® during anticoagulant therapy have been found in a review of the literature. (These, in addition to 2 previously unreported cases, 22 and 23, are summarized in the table.) A significant number of fatalities has occurred in patients with subacute bacterial endocarditis, with death usually due to hemorrhage into the brain. Of 15 patients with subacute bacterial endocarditis receiv-

From the Department of Internal Medicine, University of Michigan and the University Hospital.

1. Barker, N. W.; Hines, E. A., Jr.; Kvale, W. F., and Allen, E. V.: Dicumarol; Its Action, Clinical Use and Effectiveness as an Anti-Coagulant Drug, Am. J. Med. **3**: 634 (Nov.) 1947

2. Allen, E. V.; Barker, N. W., and Waugh, J. M.: Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis (4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of Blood: Clinical Study, J. A. M. A. **120**: 1009 (Nov. 28) 1942.

3. Cosgriff, S. W.: Present Status of Thromboembolism, Am. J. Med. **3**: 740 (Dec.) 1947. Lehmann, J.: Thrombosis: Treatment and Prevention with Methylene-Bis (4-Hydroxycoumarin), Lancet **1**: 611 (May 15) 1943.

4. Thorsen, G.: Dicoumarol Poisoning with Relapse: Report of a Case, Lancet **2**: 420 (Sept. 20) 1947.

5. (*a*) Thorsen,[4] Cahan, A.: Hemorrhage and Purpura Caused by Dicumarol: Report of a Case, New England J. Med. **228**: 820 (June 24) 1943. (*b*) Rosenbloom, D., and Crane, J. J.: Massive Hematuria Due to a Dicumarol Overdosage, J. A. M. A. **132**: 924 (Dec. 14) 1946. (*c*) Townsend, S. R., and Mills, E. S.: Effect of Synthetic Hemorrhagic Agent, 3,3'-Methylenebis (4-Hydroxycoumarin) in Prolonging Coagulation and Prothrombin Time in Human Subject, Canad. M. A. J. **46**: 214 (March) 1942. (*d*) Crawford, T., and Nassim, J. R.: Unusual Response to Dicumarol Therapy, Lancet **2**: 404 (Sept. 23) 1944. (*e*) Lucia, S. P., and Aggeler, P. M.: Treatment of Dicoumarol-Induced Hypoprothrombinemic Hemorrhage with Vitamin K1 Oxide, Proc. Soc. Exper. Biol. & Med. **56**: 36 (May) 1944. (*f*) Bruzelius, S.: Dicoumarin in Clinical Use: Studies on Its Prophylactic and Therapeutic Value in the Treatment of Thrombo-Embolism, Acta chir. Scandinav. (supp. 100), **92**: 1, 1945. (*g*) Draper, A. J.: Dicumarol Poisoning, J. A. M. A. **136**: 171 (Jan. 17) 1948.

6. Hendrick, J. W., in discussion on Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism, J. A. M. A. **133**: 1276 (April 26) 1947.

ing anticoagulants, as reported by Priest,[7] 1 (case 14) suffered a massive cerebellar hemorrhage three days after a course of penicillin combined with dicumarol® had been started; heparin was being used in a second case terminated by fatal cerebral hemorrhage. Two deaths, only 1 of which has been reported,[8] have occurred in the University Hospital during administration of heparin with chemotherapy (sulfonamide drugs) to patients with subacute bacterial endocarditis. Necropsy, in each instance, revealed the presence of cerebral hemorrhage.

A significant number of deaths has followed massive hemorrhage into the gastrointestinal tract from a surgical wound or an ulcerative lesion of the mucosa (benign or malignant). Fatal hemorrhage (case 7) was associated with the use of dicumarol® in a patient in whom a dissecting aneurysm of the aorta had been mistaken for a pulmonary embolism. Inability to differentiate a dissecting aneurysm of the aorta from a pulmonary embolism or acute myocardial infarction, with the associated hazard of anticoagulant therapy, has been emphasized by Cosgriff.[3]

Deaths Attributed to Dicumarol® During Anticoagulant Therapy

Case No.	Author	Year	No. of Patients in Series	Indications for "Dicumarol"	Autopsy	Cause of Death
1	Bruzelius [5f]	1942	1599	Venous thrombosis associated with abdominal neoplasm	Yes	Hemorrhagic diathesis; prothrombin index of 12 per cent
2	Bruzelius [5f]	1942	1599	Bladder neoplasm and postoperative venous thrombosis	Yes	Hemorrhagic diathesis; prothrombin index of 18 to 30 per cent
3	Butsch and Stewart *	1942	150	Employed in presence of inoperable carcinoma of stomach	?	Fatal hematemesis
4	Fabraeus [b]	1943	...	?	?	Fatal hematemesis
5	Wasserman and Stats †	1943	71	Embolus to femoral artery	?	Hemorrhage into rectum and from amputation stump, prothrombin index at 7 per cent; death despite five transfusions
6	Evans ‡	1944	56	Chronic deep femoral thrombosis after second stage sympathectomy	Yes	Hemorrhage into abdominal wall wound, retroperitoneal tissue; bloody pulmonary edema
7	Evans ‡	1944	56	Dissecting aneurysm of aorta mistaken for postoperative pulmonary embolism	Yes	Petechial hemorrhage into pericardium; stomach full of blood; prothrombin index 10 per cent
8	Shlevin and Lederer [11]	1944	...	Thrombosis of retinal vein	Yes	Fatal widespread uncontrollable hemorrhage
9	Davidson, Freed and MacDonald §	1945	11	?	?	Sudden death from severe hematemesis; coagulation time day prior to death elevated to 18½ minutes
10	LeFevre ‖	1945	93	Subacute bacterial endocarditis	?	Cerebral hemorrhage associated with increased prothrombin time
11	Meyer and Thill ¶	1945	11	Subacute bacterial endocarditis	?	Died after a few days of therapy, possibly from cerebral hemorrhage
12	Glueck #	1945	44	Subacute bacterial endocarditis	Yes	"Two plus" hemorrhage; death probably due to cerebral hemorrhage
13	Glueck #	1945	44	Subacute bacterial endocarditis	No	Purpura; death probably due to cerebral hemorrhage
14	Priest, Smith and McGee [7]	1946	15	Subacute bacterial endocarditis	Yes	Destruction left cerebellar hemisphere by hemorrhage, on third day of therapy
15	Barker and co-workers [1,2]	1942	1983	Subacute bacterial endocarditis	No	Clinical picture of cerebral hemorrhage
16	Barker and co-workers [1,2]	1947	...	Subacute bacterial endocarditis	Yes	Extensive widespread hemorrhage
17	Barker and co-workers [1,2]	....	...	? prophylactically, in inoperable gastric carcinoma	?	Hemorrhage during moderately severe prothrombin deficiency
18	Barker and co-workers [1,2]	1942 1947	1983	Prophylactically, after resection of duodenal neoplasm	No	Fatal gastrointestinal hemorrhage on 15th postoperative day with prothrombin concentration 30 per cent of normal
19	Barker and co-workers [1,2]	....	...	Venous thrombosis 15 days postoperative gastroduodenostomy for jejunal ulcer	Yes	Fatal bleeding from recent duodenal ulcer with essentially normal prothrombin concentration
20	Allen, Linton and Donaldson **	1947	102	Prophylactically after gastric resection	Yes	Sudden death 10th postoperative day; possibly due to cerebral hemorrhage
21	Wilson ††	1947	...	Venous thrombosis and pulmonary embolism	....	Hemorrhagic diathesis
22	Duff ‡‡	1947	250	Recent occlusion retinal artery in hypertensive patient	No	Sudden death, probably due to cerebral hemorrhage, prothrombin concentration less than 5 per cent
23	Duff and Shull (this article)	1948	...	Venous thrombosis lower extremities	Yes	Fatal widespread uncontrollable hemorrhage

* Butsch, W. L., and Stewart, J. D.: Clinical Experiences with Dicoumarin: 3,3'-Methylenebis (4-Hydroxycoumarin), J. A. M. A. **120**: 1025 (Nov. 28) 1942.

† Wasserman, L. R., and Stats, D.: Clinical Observations on Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), Am. J. M. Sc. **200**: 466 (Oct.) 1940.

‡ Evans, J. A.: Dicumarol Therapy in Thrombotic Emergencies, New England J. Med. **230**: 131 (Feb. 3) 1944; correction, ibid. **230**: 283 (March 9) 1944.

§ Davidson, C. S.; Freed, J. H., and MacDonald, H.: Effect of Vitamin K_1 Oxide upon Anticoagulant Properties of Dicumarol, Am. J. M. Sc. **210**: 634 (Nov.) 1945.

‖ LeFevre, F. A.: Effect of 3,3'-Methylene-Bis (4-Hydroxycoumarin) (Dicumarol) on Prothrombin and Coagulation Times of the Blood (Three Year Summary), Cleveland Clin. Quart. **12**: 98 (April) 1945.

¶ Meyer, O. O., and Thill, C. J.: Penicillin and Dicumarol and Penicillin in Treatment of Subacute Bacterial Endocarditis, Proc. Central Soc. Clin. Research **18**: 31, 1945.

Glueck, H. I.: Clinical Use of Anticoagulants, Ohio State M. J. **41**: 714 (Aug.) 1945.

** Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism, J. A. M. A. **133**: 1268 (April) 1947.

†† Wilson, S. J.: Differences During Dicumarol Therapy in Quick and Russell Viper Venom Methods for Prothrombin Determination, Proc. Soc. Exper. Biol. & Med. **66**: 126 (Oct.) 1947.

‡‡ Duff, I. F.: The Effectiveness of Anticoagulant Therapy as Observed in 303 Cases, to be published.

7. Priest, W. S.; Smith, J. M., and McGee, C. J.: Effect of Anticoagulants on Penicillin Therapy and Pathologic Lesions of Subacute Bacterial Endocarditis, New England J. Med. **235**: 699 (Nov. 14) 1946.

8. Field, H., Jr.; Hoobler, S. W., and Avery, N. L.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. **202**: 798 (Dec.) 1941.

We have had 1 fatality (case 22) attributable to dicumarol® among 273 patients in whom we have supervised anticoagulant therapy.[8a] This patient, a 43 year old white woman, was referred to the University Hospital for evaluation of her hypertension. There was a history of a cerebrovascular accident about ten months before admission. During the course of her studies, anticoagulant therapy was undertaken because of an acute occlusion of a retinal artery; heparin, received initially, was supplemented by dicumarol.® Dicumarol® was discontinued on the eleventh day of treatment after a total of 2.0 Gm. had been administered. The prothrombin level (Quick procedure) had been satisfactorily controlled between 30 to 20 per cent of normal concentration until the thirteenth day, when it suddenly dropped to less than 5 per cent of normal concentration. At this time the patient complained of dizziness and frontal headache; shortly thereafter she lapsed into coma with signs of a left hemiplegia and meningeal irritation. Seventy-two milligrams of vitamin K (hykinone®) were given intravenously; death occurred about four hours after the onset of symptoms. Permission for an autopsy was not obtained. Despite the lack of objective bleeding, a cerebrovascular accident is assumed to have been the cause of death. We have felt that the association of this accident with the excessive hypoprothrombinemia may well have been more than coincidental.

The absolute necessity of reliable laboratory facilities to guide the administration of dicumarol® is clearly illustrated in case 21. The patient, who suffered from thrombophlebitis and pulmonary emboli, died in a state of hemorrhagic diatheses during dicumarol® therapy. An average dose of 240 mg. of dicumarol® administered daily for fourteen days had failed to increase the prothrombin to the desired therapeutic level, as measured by the technic employing Russell viper venom as thromboplastin. Subsequent investigation disclosed the method insensitive to decided changes in prothrombin levels as evident when tested by the Quick procedure.

Particularly unfortunate have been those fatalities occurring when dicumarol® has been administered to patients without the benefit of prothrombin determinations. Fahraeus [9] (as noted by Thorsen [4]) reported a death from gastric bleeding (case 4) after 250 mg. of dicumarol® had been given daily for ten days without estimation of the prothrombin time. Smith,[10] commenting on the inadvisability of use of the drug when laboratory facilities are unavailable, mentioned a "disastrous result in one case when a dose of 250 mg. of dicumarol raised the prothrombin time to 9 minutes." Shlevin and Lederer (case 8) reported [11] the first case with postmortem observations of uncontrollable hemorrhage after dicumarol® therapy. This patient, prior to coming into their hands, had received 100 mg. of dicumarol® daily for twenty-one days for a retinal vein thrombosis; therapy was uncontrolled by prothrombin determinations. We have recently seen a similar case (case 23) in which large doses of dicumarol® had been administered daily for about thirty-seven days with no laboratory control.

8a. Since completion of this report a second fatality due to dicumarol has occurred in the University Hospital. This patient, a 79 year old woman, likewise had severe hypertension and had sustained cerebrovascular accidents several months prior to admission. Prophylactic dicumarol, instituted subsequent to a femoral neck fracture, was associated with a sudden drop in prothrombin to a low level coincident with which the patient sustained a fatal cerebral hemorrhage. An autopsy was not permitted. The occurrence of these two fatalities stresses the hazard of administering dicumarol to patients with severe hypertension, particularly if there is a past history of cerebrovascular accidents.

9. Fahraeus, R.: Svenska läk-tidning **40**: 2859, 1943.

10. Smith, E., and Kaufmann, J.: Use of Dicumarol and Vitamin K in Urological Cases, J. Urol. **52**: 353 (Oct.) 1944.

11. Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicumarol Therapy with Autopsy Findings, Ann. Int. Med. **21**: 332 (Aug.) 1944.

REPORT OF A CASE

A 36 year old white woman was first admitted to the University Hospital as an emergency patient at 2 p. m. on Dec. 29, 1947. According to the accompanying letter from the referring physician, the patient had complained of violent headaches and pain in the shoulders, neck and back. These symptoms were associated with extreme weakness, nausea, lower abdominal cramps, hemoptysis and vaginal bleeding. The past history revealed that she had had pulmonary tuberculosis for which she had received sanatorium care for eight months in 1928; three months prior to the present illness she had had a normal chest roentgenogram and a negative reaction to a tuberculin test. An appendectomy had been performed in 1945. The family history was irrelevant.

According to her husband, from whom the details of the present illness were obtained, dicumarol® had been administered because of the recent onset of pain and swelling of both legs. Treatment with the drug was started on Nov. 20, 1947 and continued until December 27 in a dosage thought to be 300 mg. daily. In this period a total of about 11.1 Gm. is estimated to have been ingested; the prescription had been refilled on three different occasions, despite the fact that the condition of her legs had improved. She had also received orally an unknown amount of penicillin; no information was available concerning the use of sulfonamide drugs. In this period she was up and about the home; no laboratory studies were carried out. Nothing untoward took place until about December 22, when there was the onset of blood-streaked sputum. Two days later, because of nausea and vomiting, dicumarol® had been withheld and the patient was put to bed. On December 27, she complained of a severe and progressive headache. The day before admission the patient became irrational, bleeding began from the mouth and vagina, and there was gross hematuria. There had been no epistaxis.

On admission to the Medical Service, the patient was obviously acutely and critically ill, being semicomatose and disoriented. Though well developed and nourished, she was in a state of peripheral vascular collapse, with the blood pressure at 80 systolic and 60 diastolic, the pulse rate 130, the respirations 15 per minute and the temperature 98.6 F. There was a small amount of blood-streaked sputum and moderate bright red vaginal bleeding. Submucosal ecchymoses were observed on the tongue, gums and cheeks and in the pharynx. There were ecchymoses on the extremities, which measured up to 3 cm. in diameter; petechiae were not observed; the result of the tourniquet test was negative. Bleeding into the fundi was not seen. A systolic murmur was heard over the entire precordium. The neurologic examination revealed fixation and constriction of the left pupil, ptosis of the right eyelid and a left-sided facial paralysis with deviation of the tongue to the left. There was nuchal rigidity. Kernig's and Brudzinski's signs were positive. There was weakness of the left arm and leg; the left achilles reflex was hyperactive; ankle clonus and the Babinski sign were present bilaterally. The patient was unresponsive to light, touch or vibration. Deep pain produced a withdrawal reaction.

It was possible to do only the more urgent laboratory studies. The urine contained gross blood. Blood hemoglobin measured 9 Gm. (Sahli). The bleeding time (Ivy method) was prolonged to 7 minutes; the clotting time (Lee and White method) was prolonged to 48 minutes; clot retraction was decidedly deficient at the end of 2 hours. The prothrombin time (Quick procedure) was prolonged to 500 seconds in one determination and 800 seconds in another, with the normal control time of 16 seconds. The amount of prothrombin was so depleted that expression in terms of percentage of concentration, from the standard dilution curve, was impossible. The result of the postmortem Kahn serologic test was positive.

Heroic efforts were made to control the inevitable course of the hemorrhagic diatheses. With 1,000 cc. of blood and 1,500 cc. of 5 per cent dextrose, the peripheral vascular collapse was temporarily controlled, the blood pressure eventu-

ally rising to 130 systolic and 78 diastolic. Seventy-two milligrams of vitamin K (hykinone®) was administered intravenously every three hours, a total of 222 mg. being received in fourteen hours. Despite some initial improvement, the patient never regained consciousness; restraints were required. Eight hours after her admission, the respirations became Cheyne-Stokes in character. Death occurred fifteen hours after her admission to the hospital, and three days after the dicumarol® therapy had been discontinued. The prothrombin time of blood obtained at autopsy (four hours after death) was 85 seconds, as compared with the normal control time of 16 seconds. The prothrombin concentration was estimated to have been less than 5 per cent of normal.

Postmortem Examination.—Gross Pathologic Observations: The pertinent gross pathologic observations were as follows: The head and neck were essentially normal, except for the presence of considerable serosanguineous exudate in the oral pharynx. There were multiple puncture wounds on the arms, antecubital fossae and buttocks, in association with some of which there were diffuse hematomas. There was an old lower abdominal midline scar.

The brain weighed 1,160 Gm. The meningeal vessels were congested. Beneath the right inner meninges was a diffuse hematoma over the entire right hemisphere; the left meninges were congested. The right hemisphere was swollen and edematous; sulci were narrowed; gyri flattened. There was a lemon-sized hemorrhagic softened necrotic lesion in the right parietotemporal region near the external cortical surface and ventricle. The left hemisphere was edematous and congested and contained multiple petechial hemorrhages throughout. The ependymal surface of the right and left lateral ventricles showed congestion. The choroid plexus was hemorrhagic and cystic. Examination of the lumbar part of the spinal cord revealed a diffuse hematoma beneath the pia-arachnoid.

The pleural cavities contained no excess free fluid and were obliterated bilaterally along the posterior gutters by dense fibrous adhesions. The left lung weighed 550 Gm. The cut surface disclosed acute passive congestion. The right lung weighed 600 Gm.; its gross appearance was comparable with the left. There was severe congestion of the mucosa of the trachea, bronchi and esophagus; the bronchi contained a moderate amount of serosanguineous exudate. The thoracic and abdominal aorta revealed slight atherosclerosis of the intima.

There were 40 cc. of serosanguineous fluid in the pericardial sac. The heart weighed 240 Gm. The thickness of the left and right ventricular walls was normal, with normal epicardial and endocardial surfaces. A few petechial hemorrhages were present in the right ventricle and right atrium; no thrombi were found. The dimensions of the mitral, tricuspid, pulmonary and aortic valves were normal. A few yellow nodules were present on the leaflets of the mitral and tricuspid valves and on the free margins of the aortic cusps. A diffuse hematoma was present in the atrial wall at the entrance of the superior vena cava. The coronary arteries revealed slight atherosclerotic changes.

The abdominal cavity contained approximately 100 cc. of fluid blood distributed over loops of large and small intestines; fibrous adhesions were present. The peritoneum, which was pinkish purple, contained multiple petechial hemorrhages throughout. The spleen weighed 100 Gm.; the cut surface showed a purplish red splenic pulp with well marked malpighian corpuscles; there was no infarction. The mucosa of the large and small intestines was congested but not hemorrhagic. The appendix was absent. Serosal hemorrhages were present in the stomach. The pancreas weighed 100 Gm. and was free of hemorrhage. The liver measured 6.5 cm. below the ensiform and 2 cm. below the right costal margin; its weight was 1,540 Gm. The external, and especially the lower, surface showed diffuse ecchymotic hematomas in the capsule. The cut surface disclosed a mottled yellow-pink appearance. About the blood vessels of the hepatic trinities, outside their walls, was a dark purple hematoma. The wall of the gallbladder contained a diffuse hematoma. The left adrenal weighed 12 Gm. A diffuse hematoma was present about the gland and in the periadrenal tissue. There was slight autolysis of the medulla but no hemorrhage. The right adrenal, which weighed 16 Gm., showed similar changes. The left kidney weighed 220 Gm., and the capsule stripped with ease. There were multiple petechial hemorrhages, and the cut surface disclosed acute passive congestion. The pelvic mucosa was severely congested, and a diffuse hematoma outside the mucosa extended 6.5 cm. down the ureter. Hematomas were also present within the ureteral mucosa. The gross appearances of the right kidney, which weighed 190 Gm., and the ureter were similar to those on the left, including the same distance of hemorrhage from the pelvic mucosa. There was congestion of the mucosa of the rectum, urethra and bladder, the latter showing a few petechial hemorrhages. There was cystic cervicitis. Fluid blood was present over the surface of the endometrium; a small myometrial leiomyoma was present. The ovaries were cystic; the uterine ligaments contained a diffuse hematoma.

Microscopic Pathologic Observations: The examination of the spinal cord revealed congestion with slight subarachnoid hemorrhages. The essential lesions found in the brain consisted of small hemorrhages by diapedesis, which were most numerous in the white matter of the cerebral hemispheres but were also present in the cerebral cortex, brain stem and white matter of the cerebellum. Associated with this there was distension of the subarachnoid spaces by fresh blood and recent bleeding at the site of the softening in the right parietotemporal region. There was also severe dilatation of the arterioles and capillaries and some perivascular rarefaction of tissue. In some perivascular regions there was old blood pigment engulfed by histocytes. The secondary effects of the hemorrhagic disturbance consisted of severe edema of the parenchyma, manifested by distension of the interstitial spaces, swelling of the oligodendroglia and shrinkage of cortical neurons. There was also a mild proliferation of microglia and astrocytes in the white matter.

There was hemorrhage in the epicardial fat. The aorta showed slight atherosclerotic changes with calcification of the media. Acute congestion and edema of the lungs were present, with severe hemorrhages by diapedesis. Atelectasis, emphysema and fibrous pleuritis were observed. The trachea showed hemorrhages into the adventitia; there were hemorrhages into the serosa of the esophagus and stomach.

The thymus contained persistent lymphoid tissue, and fatty atrophy was present. The spleen revealed acute passive congestion. There were hemorrhages into the mesentery of the small intestines, and wandering cells were increased. The colon was normal except for increased mucin. There was congestion of the pancreas with slight hemorrhage by diapedesis. Extensive hemorrhage was present at the hilus of the liver and over the capsule with central brown atrophy and slight lipidosis of the parenchyma (fat stain). The gallbladder showed extensive hemorrhage beneath the serosa, with a subacute inflammatory infiltration, including eosinophils, and thrombosed veins. Periadrenal hemorrhage was present with leukocytic infiltration and loss of lipids from the inner zone of the cortex (fat stain). The kidneys were congested, and hemorrhage was present in the distal convoluted tubules. There was vasculitis in the pelvic adipose tissue, with abundant eosinophils. Hemorrhage had occurred beneath the pelvic epithelium. Slight interstitial peripelvic nephritis was present; fat stains were negative. The ureters revealed hemorrhage throughout the walls with eosinophils in an inflammatory exudate and severe mucosal congestion. Voluntary muscle showed hemorrhages in adjacent adipose tissue. Bone marrow of the ribs, sternum, and vertebral bodies, following decalcification, was hyperplastic, about 90 per cent cellular, with periosteal hemorrhages. The breasts and bladder were essentially normal.

Pathologic Diagnosis [12]: Hypinosis was observed, with cerebral, subarachnoid, cardiac, renal, hepatic, pulmonary, periosteal, retroperitoneal and cutaneous hemorrhages. Other observations were: acute passive congestion of all organs; cerebral and pulmonary edema; angiitis in the wall of the gallbladder, renal pelves and ureters, with eosinophilia; hypersensitivity reaction; slight atherosclerosis of the aorta and its branches; slight lipidosis of the liver; edentulism; fibrous pleuritis; an old

12. The gross and microscopic observations were made by the Department of Pathology and Neuropathology, University Hospital, University of Michigan, Ann Arbor.

appendectomy, and persistent thymus. There was positive reaction to a postmortem serologic test (4 plus, Kahn), indicating possible latent syphilis. A culture of blood from the heart yielded no growth.

COMMENT

Dicumarol® poisoning is characterized by hemorrhage. In cattle fed spoiled sweet clover hay, as pointed out first by Schofield [13] and later by Roderick,[14] bleeding occurred at sites of stress and was more commonly present in fascia of muscles and subcutaneous tissues, with the local blood vessels showing no pathologic changes. Schofield described gross lobular lesions in the liver to which he attributed the hemorrhagic tendency. Roderick attributed these observations to postmortem changes and found no serious impairment in hepatic function.

McCarter, Bingham, Meyer and Pohle [15] reported the pathologic observations after the administration of dicumarol.® In dogs dying of acute poisoning after massive doses of dicumarol® the outstanding morphologic evidences of toxicity were: (1) gross or microscopic hemorrhage, (2) toxic lesions of small vessels, (3) acute renal glomerular swelling and (4) toxic lymphoid tissue reactions. They particularly emphasized the presence of serious damage to the small blood vessels. No consistent lesions of the liver attributable to dicumarol® were discovered. In a series of dogs which had received dicumarol® at levels of therapeutic dosage, the only toxic tissue effect observed was in the hyperplastic reactive lymphoid tissue. In a series of 5 autopsies on human beings to whom dicumarol® in therapeutic doses had been administered, no typical lesions were observed which could be unequivocally charged to dicumarol.®

Ferraro and Roizin [16] reported histologic changes in various tissues and viscera of chicks due to dietary vitamin K deficiency with hypoprothrombinemia. A diffuse hemorrhagic diathesis was represented by small and large hemorrhagic involvement of subcutaneous tissues, muscles, joints, bone, periosteum, heart, thymus, lungs, intestines, liver, kidneys, spleen, gonads, meninges, spinal cord and brain. Notable changes in the walls of veins and arteries were emphasized, such as irregular dilatation, hypertrophy, hyperplasia and mild degeneration to complete rupture of the vessels.

Shlevin and Lederer,[11] reporting postmortem observations in a fatal case of uncontrollable hemorrhage in a human being following dicumarol® therapy, emphasized decided engorgement of all blood vessels, excepting the large trunks, which was most pronounced in the capillaries, arterioles and venules. Where the hemorrhages occurred in various tissues and organs, the vessel walls were consistently found to be intact with broad lumens. They suggested that these extravasations were due to diapedesis between cells rather than to rupture or solution of continuity of the cell walls. They reported that the liver showed many areas with distended sinuses filled with unclotted blood. This also was a prominent feature in dogs poisoned with excessively large doses of dicumarol.® [15]

Our patient demonstrated many of the aforementioned changes, in addition to gross hemorrhage into the brain, kidney and liver. The associated gross destruction of brain tissue was probably the immediate cause of death.

CONCLUSION

The most important of all contraindications to the use of dicumarol® is lack of reliable laboratory facilities for prothrombin determinations. Employment of this beneficial drug without laboratory control is hazardous and may result in fatal widespread hemorrhage.

Caution should be observed in the administration of dicumarol® to patients with severe hypertension, particularly if there is a past history of cerebrovascular accidents.

13. Schofield, F. W.: A Brief Account of a Disease in Cattle Simulating Hemorrhagic Septicaemia Due to Feeding Sweet Clover, Canad. Vet. Rec. **3**: 74, 1922; Damaged Sweet Clover: The Cause of a New Disease in Cattle Simulating Hemorrhagic Septicemia and Blackleg, J. Am. Vet. M. A. **64**: 553 (Feb.) 1924.

14. Roderick, L. M.: The Pathology of Sweet Clover Disease in Cattle, J. Am. Vet. M. A. **74**: 314 (Feb.) 1929; Problem in Coagulation of Blood: "Sweet Clover Disease of Cattle," Am. J. Physiol. **96**: 413 (Feb.) 1931.

15. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylenebis (4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**: 563 (Oct.) 1941. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the Hemorrhagic Agent 3,3'-Methylenebis (4-Hydroxycoumarin): IV. The Pathologic Findings After the Administration of Dicumarol, Am. J. Path. **20**: 651 (May) 1944.

16. Ferraro, A., and Roizin, L.: Hemorrhagic Diathesis Experimentally Induced by Deficiency in Vitamin K: A Histopathologic Study, Am. J. Path. **22**: 1109 (Nov.) 1946.

EVALUATION OF AEROSOL–NEGATIVE PRESSURE THERAPY

Given Once Daily in Chronic Purulent Sinusitis

EDUARDO R. PONS Jr., M.D.
WALTER M. GLASS, M.D.
and
BETTINA GARTHWAITE, M.D.
New York

The purpose of this investigation is a critical evaluation of aerosol alternating negative pressure therapy given once daily in cases of chronic purulent sinusitis.

The inhalation route for administration of various medicaments, such as bronchodilator and bronchovasoconstrictor drugs, and in more recent years chemotherapeutic and antibiotic groups of drugs, is now well established in the treatment of certain types of bronchopulmonary disease.[1] Inhalational therapy of diseases of the upper part of the respiratory tract has also been extended to include antibotic aerosols. Some favorable clinical results were reported by Vermilye [1j] in cases of acute sinusitis and acute pharyngitis and in acute exacerbations of chronic sinusitis. However, it was first demonstrated by Barach and his co-workers [2] that alternating application of negative pressure with inhalation of penicillin aerosol was necessary to insure

This study was made possible by a grant from the Josiah Macy Jr. Foundation.

From the Departments of Medicine and Otolaryngology of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York.

1. (*a*) Graeser, J. B., and Rose, A. H.: Inhalation of Epinephrine for Relief of Asthmatic Symptoms, J. Allergy **6**: 415-420 (July) 1935. (*b*) Richards, D. W., Jr.; Barach, A. L., and Cromwell, H. A.: Use of Vaporized Bronchodilator Solutions in Asthma and Emphysema: A Continuous Inhalation Method for Severe Asthmatic States, Am. J. M. Sc. **199**: 225-232 (Feb.) 1940. (*c*) Barach, A. L.: Physiologic Therapy in Respiratory Diseases, Philadelphia, J. B. Lippincott Company, 1948. (*d*) Castex, M. R.; Capdelhourat, E. L., and Laverello, A.: Nuevo tratamiento de las supuraciones bronchopulmonares: Acción curativa de un preparado sulfamidico nebulizado, Rev. Asoc. méd. argent. **55**: 85-89 (Feb. 15-28) 1941. (*e*) Bryson, V.; Sansome, E., and Laskin, S.: Aerosolization of Penicillin Solutions, Science **100**: 33-35 (July 14) 1944. (*f*) Barach, A. L.; Silberstein, F. H.; Oppenheimer, E. T.; Hunter, T. H., Soroka, M.: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**: 485-509 (April) 1945. (*g*) Segal, M. S.; Levinson, L., and Miller, D.: Penicillin Inhalation Therapy in Respiratory Infections, J. A. M. A. **134**: 762-770 (June 28) 1947. (*h*) Garthwaite, B., and Barach, A. L.: Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis, Am. J. Med. **3**: 261-293 (Sept.) 1947. (*i*) Olsen, A. M.: Nebulization Therapy in Bronchiectasis, J. A. M. A. **134**: 947-953 (July 12) 1947. (*j*) Vermilye, H. N.: Aerosol Penicillin in General Practice, J. A. M. A. **129**: 250-257 (Sept. 22) 1945.

2. Barach, A. L.; Garthwaite, B.; Soroka, M., and Anderson, F. F.: An Apparatus for the Introduction of Penicillin Aerosol into the Nasal Accessory Sinuses with a Case Report of a Patient with Chronic Sinusitis, Ann. Int. Med. **24**: 97-103 (Jan.) 1946.

the introduction of penicillin into the maxillary sinuses and thereby prove efficacious in therapy of chronic sinusitis.

In cases of chronic purulent sinusitis such treatment performs four functions: shrinkage of congested mucous membrane, drainage of exudate from the paranasal sinuses during the phase of suction, ventilation of the sinuses with oxygen or air and introduction of antibiotic aerosol to the diseased site.

Barach and his co-workers previously reported the clinical usefulness of nasal penicillin aerosol combined with alternating negative pressure in therapy of acute and chronic sinusitis.[3] The original apparatus has been modified into a simplified unit.[4] Experimental evidence has been presented suggesting that ventilation, drainage and deposition of penicillin aerosol occur in the paranasal sinuses when this apparatus is used. An oxygen flow of 5 to 8 liters per minute produces, by means of a glass venturi tube, a negative pressure of approximately 60 to 70 mm. of mercury in the maxillary antrums and slightly higher pressures in the nasal passages. Higher oxygen flows result in progressively higher negative pressures within the nose but very slight increase in negative pressure within the antrums, necessitating the conclusion that above a certain negative pressure the increased suction is not transmitted to the antrums because of closure of the ostiums and therefore defeats the purpose of the suction phase of treatment. In subjects with oroantral fistulas, demonstration of penicillin in the antrum was possible after inhalation of the drug in aerosol form when the sinus negative pressure apparatus was used. It was shown that some of the penicillin aerosol condensed inside the nasal passageway and was sucked into the antrum in liquid form. Finally, it was demonstrated that penicillin introduced into the antrum in aerosol form is actually deposited therein and can be recovered in later irrigation for at least two hours after completion of the aerosol treatment.[3]

McAuliffe and Mueller [5] have described a modification of this apparatus, which can be used in otolaryngologic practice with any standard vacuum and pressure pump to introduce penicillin aerosol into the paranasal sinuses by using calibrated suction and pressure. These authors reported that the method gave good results in infections of the upper part of the respiratory tract, including infections of the paranasal sinuses.

In evaluating the effect of any therapy of sinusitis it must be realized that acute purulent sinusitis is usually a self-limited disease and sooner or later resolves completely in the majority of instances, no matter which of the usual forms of treatment are employed. Some cases of chronic disease are also subject to partial remissions and exacerbations of symptoms. Even in chronic purulent sinusitis no 2 cases are alike. Evaluation of this group as a whole is complicated by the differences in the individual cases because of factors such as the severity of symptoms, duration of the disease and appearance of the physical signs. One patient may complain of only moderate postnasal discharge and nasal congestion over a period of a year or two, present minimal signs of sinusitis and return a few mucopurulent clumps on antral irrigation; while another patient may complain of profuse anterior and posterior nasal discharge, nasal blockage, headache, cough and expectoration over a period of many years, give a history of repeated sinus irrigations and surgical procedures and present 4 plus foul broken-down pus on antral irrigations. Allergic factors also contribute to the variability of the disease—some cases are primarily allergic in nature with a secondary bacterial infection, while other cases are primarily bacterial in nature with a superimposed bacterial allergy. There are other cases in which it is impossible to determine whether the allergy or the infection is the primary cause of the disease. Recently, emphasis has been placed on the importance of psychosomatic influences on the behavior of diseases involving the nasal mucous membranes.[6]

Since the principles of shrinkage and suction in themselves are well established otolaryngologic methods of treatment, we have also attempted in the present study to analyze more accurately the role of the antibiotic versus the role of shrinkage and drainage. The major portion of this report deals with the results of therapy in two comparable series of cases of sinusitis treated with this method in identical fashion except for the omission of penicillin in the group that served as a control. In addition, the experience with streptomycin aerosol in gram-negative sinus infections is presented. Clinical impressions on the practical applications of the method in general and rhinologic practice are discussed, and indications for its use are postulated.

METHODS

Selections were made from patients of the Nose and Throat Department of Vanderbilt Clinic. In selecting cases of chronic purulent sinusitis for inclusion in the series all the following criteria had to be satisfied: (1) a history of continuous symptoms of sinusitis for at least six months prior to treatment, (2) evidence of infection of the nasal mucosa with the presence of pus in the nose either before or after shrinkage, (3) cloudiness of one or more sinuses on transillumination, (4) roentgen evidence of sinusitis, (5) purulent returns on antral aspiration and (6) the appearance of pathogens on culture. A history of the disease was obtained in all patients, with special emphasis on allergic factors, past or associated diseases of the respiratory tract and previous otolaryngologic therapy. A careful examination of the nose, nasopharynx and oropharynx with transillumination of the sinuses was done in each case in order to study the condition of the nasal mucous membrane, to detect signs of allergy, to document the existence of purulent infection and to exclude factors that might interfere with drainage from the paranasal sinuses (polyps, deviated septum, hypertrophied turbinates, etc.). If the sinus ostiums were mechanically blocked, surgical correction was performed prior to acceptance of the patient for therapy.

Routine sinus roentgen examinations were made in all cases. Following this, cocainization of the inferior meatus, antral puncture with a trocar and aspiration of the antral contents were done. The latter was made with a sterile syringe and served both to obtain mate-

3. Barach, A. L.; Garthwaite, B.; Rule, C.; Talbot, T. R., Jr.; Kernan, J. D.; Babcock, J., and Browne, G.: Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis, Am. J. Med. **1**: 268-290 (Sept.) 1946.

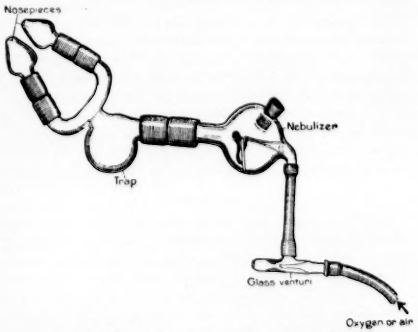
4. Barach, A. L.; Rumsey, C. C.; Soroka, M., and Rader, D.: A Simplified Technic of Treating Sinusitis with Penicillin Aerosol with a Description of a Foot Pump for Economical Nebulization of Penicillin and Other Therapeutic Aerosols, New York State J. Med. **47**: 1498-1500 (July 1) 1947.

5. McAuliffe, G. W., and Mueller, G. C.: Aerosol Penicillin Administered in Paranasal Sinusitis with Balanced Suction and Pressure, Arch. Otolaryng. **46**: 67-71 (July) 1947.

6. Fowler, E. P., Jr.: Personal communication to the authors. Holmes, T. H.; Goodell, H.; Wolf, S., and Wolff, H. G.: Changes in the Nasal Function Associated with Variations in Emotional State and Life Situation, Tr. Am. Acad. Ophth. **51**: 449-460 (May-June) 1947.

rial for bacteriologic study directly from the antrums and further to establish objectively the presence of purulent infection. This was followed in most cases by a diagnostic antral irrigation, in order to note the amount and nature of the antral contents. In a few patients, i. e., children and hypersensitive persons, nasal cultures of the purulent overflow from the sinuses were taken after prior shrinkage and cleansing of the nasal passages.

The apparatus used for treatments was the simplified one developed by Barach and his co-workers,[4] consisting of a glass nebulizer, trap and olive-tipped nose pieces which are connected to a source of oxygen or compressed air by means of rubber tubing into which a glass venturi tube is inserted (figure).[7] In using the apparatus, the patient holds the nose pieces tightly in the nostrils. By holding the thumb over the open end of the venturi, oxygen or air is forced into the nebulizer, producing the aerosol which flows into and fills the nasal cavities. The patient gently breathes through his mouth three times, after which he removes his thumb from the open end of the venturi, closes his mouth and swallows. The oxygen or air now



Drawing of the apparatus used in this study.

passes out of the open end of the venturi, creating a negative pressure in the apparatus, which is transmitted to the paranasal sinuses when the palate is closed in the act of swallowing. The venturi is then closed again with the thumb and the procedure repeated until aerosolization of solution in the nebulizer is completed. When used in alternation with nebulization, suction from the venturi allows alternating partial emptying and filling of the paranasal sinuses with oxygen or air heavily laden with nebulized particles.

All treatments were given once daily, six days a week, and were continued up to four weeks. All patients were individually instructed in the correct use of the apparatus. The great majority of patients were treated in the clinic for the entire length of treatment and were under close supervision at all times. Only a few patients were allowed to take treatment at home, after preliminary training consisting of at least one week of daily clinic treatments.

After initial antral culture, with bacterial sensitivity tests in some instances, the appropriate antibiotic was selected. Penicillin treatments consisted of 250,000 units crystalline penicillin[8] in 2 cc. of 1 per cent ephedrine sulfate in saline solution, with rinses of 1.0 and 0.5 cc. distilled water each. Streptomycin[9] dosage was 0.5 Gm. of the calcium chloride complex, in 2 cc. of 1 per cent ephedrine sulfate in saline solution with 1.0 and 0.5 cc. distilled water rinses. Ephedrine treatments were identical except for the omission of antibiotics. Inactivated penicillin was used in addition to the ephedrine preparation in 5 control cases in which there was a decided psychosomatic component. Nebulization of solutions was effected with oxygen at 6 liters per minute flow except for a few of the patients treated at home who used a foot pump instead of oxygen as a source of power for nebulization. The time for a single treatment averaged thirty minutes. By keeping the volume of solutions identical and by using the same flow and uniform technic, we maintained the degree and length of time of application of negative pressure approximately equal in all cases.

In each patient, symptoms of headache, coryza, nasal obstruction, amount and nature of anterior and posterior nasal discharge, cough and expectoration were followed daily, as well as signs of possible toxic reactions. Examinations of the nose and throat with transillumination of the sinuses were conducted weekly, and in some cases interval sinus roentgenologic examinations were done. At the end of treatment roentgenograms were again made and compared with previous ones. A final nose and throat examination, antral puncture, aspiration of antral contents for culture and a final diagnostic irrigation were done, the latter to note any change in the amount and nature of the antral contents. An attempt was made to follow all patients' symptoms and signs of sinusitis during the first month after treatment and at later intervals.

It must be remembered that the program followed in this series of clinic patients is probably not the ideal one for obtaining optimal results. It is believed that treatments given several times daily would be superior in terms of continued relief of nasal obstruction and maintenance of a therapeutic local concentration of antibiotic drug within the sinuses. The one treatment a day method was used in this study because it was the most practical method that afforded strict daily control and supervision of individual clinic patients. It was also felt that administration of one massive treatment daily, six days a week for one month would be comparable to the use of four smaller daily treatments of over a two week period.[3]

Except for the separation of cases in which there were allergic manifestations, further breakdown of the series to consider factors such as duration of symptoms, severity of the disease and nature of antral contents was found to be impractical, as it resulted in groups containing very small numbers of cases.

In each case, separate evaluation was made of symptoms, physical signs, roentgenograms, antral contents and bacteriologic aspects. Improvement in the symptoms, physical and roentgen appearance was classified as being slight or none, moderate or decided, and the usual margin of human error prevailed in deciding in which category the individual cases belonged. In general those patients that at the end of treatment presented a normal appearing nose, had no symptoms and a normal roentgenogram were tabulated as showing decided improvement in each category. Those patients that did not have complete normality in each respect

7. This apparatus may be obtained from the Inhalational Equipment Company, 248 East 119th Street, New York, the Oxygen Equipment Mfg. Corp., 405 East 62nd Street, New York, and the Vaponefrin Co., 6812 Market Street, Upper Darby, Pa.

8. Supplied by Commercial Solvents Corporation and Premo Pharmaceutical Laboratories, Inc.

9. Supplied by Merck & Co., Inc.

were classified as showing moderate, slight or no improvement, as seemed appropriate.

The quantity and gross nature of antral contents provided another measure of therapeutic effectiveness which was termed as decided when the final irrigation was entirely clear, moderate when an initial observation of broken down pus gave way to clumps or shreds, and slight to none when no change occurred or in cases of bilateral disease when there was only partial one-sided change. Bacteriologic changes could be determined by comparison of organisms cultured from the antrum before and at the end of treatment. In summarizing these changes, cases were grouped according to disappearance of all organisms, complete or partial disappearance of gram-positive or gram-negative organisms and, finally, as no change in bacteriologic observations.

laryngologic examination revealed only the presence of a purely allergic or vasomotor rhinitis, or of deviated septums, polyps or hypertrophied turbinates. In many instances of true chronic purulent sinusitis the observation of mechanical blocking of the sinus ostiums revealed factors amenable to surgical correction without which the introduction of antibiotic aerosol into the sinuses was impossible. In some patients dental foci had to be eradicated in order to control successfully the infection. Other cases were rejected because symptoms of chronic sinusitis were found to have solely a psychosomatic basis. Many of the patients with organic sinus disease had superimposed functional complaints which further complicated evaluation of results.

1. Comparison of Penicillin and Ephedrine Control Groups (table 1).—Symptoms: About equal numbers of patients in both ephedrine-treated and penicillin-treated

TABLE 1.—*Improvement in Chronic Purulent Nonallergic Sinusitis Resulting from Aerosol Therapy with Negative Pressure*

Treatment Used	Number of Cases	A. Symptoms			B. Physical Examination			C. Roentgenogram			D. Antral Contents			
		Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Not Evaluated
Penicillin	23	8	7	8	7	8	8	3	8	12	6	4	9	4
Ephedrine sulfate	23	8	6	9	2	3	18	1	3	19	6	3	11	3

TABLE 2.—*Improvement in Chronic Purulent Allergic Sinusitis Resulting from Aerosol Therapy with Negative Pressure*

Treatment Used	Number of Cases	A. Symptoms			B. Physical Examination			C. Roentgenogram			D. Antral Contents			
		Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Not Evaluated
Penicillin	5	3	2	0	1	2	2	0	0	5	0	2	1	2
Ephedrine sulfate	7	2	3	2	1	1	5	0	1	6	0	0	5	2
Total	12	5	5	2	2	3	7	0	1	11	0	2	6	4

TABLE 3.—*Results in Streptomycin Aerosol-Negative Pressure Therapy of Chronic Sinusitis Due to Gram-Negative Infection*

Type	Number of Cases	A. Symptoms			B. Physical Examination			C. Roentgenogram			D. Antral Contents			
		Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Decided	Moderate	Slight or None	Not Evaluated
Nonallergic	6	3	1	2	0	4	2	0	1	5	1	0	1	4
Allergic	4	2	1	1	0	1	3	0	1	3	1	0	2	1
Total	10	5	2	3	0	5	5	0	2	8	2	0	3	5

RESULTS

The penicillin and ephedrine control groups number 23 patients each. In all instances, some degree of involvement of the maxillary sinuses was present. In about half the cases these were the only sinuses found to be diseased; when multiple sinus infection occurred the ethmoids were involved more often than the frontals or sphenoids. The condition in about two thirds of the cases was bilateral. The average duration of the disease was eleven years; approximately half of the patients previously had had antral irrigations and/or nasal surgical treatment with temporary or no effect on the disease. The similar incidence of all these factors in both the penicillin-treated and ephedrine-treated patients justified the assumption previously made on the basis of history, physical signs and roentgen observations, that the two groups were comparable. This was further supported by an almost equal distribution of bacterial flora in the material studied from both groups of cases.

In many patients who presented themselves with symptoms suggestive of chronic sinusitis, complete oto-

groups showed decided, moderate and slight-to-absent symptomatic improvement (table 1, A). Qualitatively, the response to treatment was also similar. Some of the patients with severe long-standing complaints showed a dramatic change in symptoms. Striking relief of chronic headache was at times seen, concomitant with drainage of purulent secretions into the trap of the apparatus. Nasal obstruction was relieved temporarily for one to six hours or longer following treatment. In many of the patients showing a favorable response, anterior and posterior nasal discharge increased during the first three or four days of treatment and decreased gradually thereafter. The diminution of postnasal drip was accompanied by reduced cough and expectoration. In patients with associated bronchopulmonary infection, a significant decrease in cough and expectoration, with loss of most of the purulent element in the sputum, occurred only in the group treated with penicillin aerosol.

Physical Observations: Seven of the penicillin-treated patients showed decided and 8 showed moderate improvement. Two of the ephedrine-treated patients

showed decided and 3 showed moderate improvement (table 1, B).

Roentgenograms: Eleven of the penicillin-treated patients showed decided or moderate improvement, while only 4 of the ephedrine control patients showed comparable changes (table 1, C).

Antral Contents: There were no over-all differences in 19 penicillin-treated and 20 ephedrine-treated patients. Half of the patients in each group showed no change in the character and amount of antral contents (table 1, D). However, of the patients showing fluid and broken down pus at the start of treatment, the condition in 5 out of 13 treated with penicillin cleared entirely, while 2 out of 11 patients treated with ephedrine showed disappearance of the antral pus.

Bacteriologic Observations: Mixed infections were found in about 60 per cent of all the cases. The commonest organisms found in the antrums in order of incidence were: Hemophilus influenzae, hemolytic Staphylococcus aureus, pneumococci and microaerophilic streptococci. The bacteriologic changes before and after treatment are summarized in table 4. Some changes in bacterial flora could be seen to occur in the control cases in which the ephedrine preparations were used, but changes tended to be more pronounced in the patients that were treated with penicillin. Only a small number of patients showed complete disappearance of all organisms at the end of treatment, 2 in the penicillin group and 3 in the ephedrine control group. Six of the penicillin group showed disappearance of all gram-positive organisms with persistence of the original, or appearance of new, gram-negative flora at the end of treatment. This also is seen in sputum cultures of patients with bronchopulmonary infection treated with penicillin aerosol.[1b] None of the ephedrine control cases showed this change. There was no bacteriologic change in 10 ephedrine control patients and in 5 patients treated with penicillin.

TABLE 4.—*Bacteriologic Changes in Chronic Sinusitis*

Type case	Nonallergic Patients		Allergic Patients	
Treatment	Penicillin	Ephedrine Sulfate	Penicillin	Ephedrine Sulfate
Disappearance of organism	2	3	..	..
Complete disappearance of gram-positive, with persistence or appearance of gram-negative flora at end of therapy	6	..	1	2
Partial disappearance of gram-positive from mixed flora at end of therapy	5	4	..	1
Appearance of gram-positive organisms	..	2	..	..
No change	5	10	3	4
No observations made	5	4	1	..
Total	23	23	5	7

Direct demonstration of the entrance of penicillin into the antrums in cases of known purulent sinusitis was possible by determination of penicillin levels in pus aspirated from the antrum immediately after a penicillin treatment. In 6 cases in which observations were made concentrations of penicillin ranging from 0 to 8.0 units per cubic centimeter of antral pus were found. Of these patients, 3, who showed 1.4, 7.0 and 8.0 units per cubic centimeter, also had improvement in antral contents and bacteriologic observations. Two patients, with 0 and 0.8 unit per cubic centimeter, showed no improvement in these respects, while in one test resulting in a penicillin level of 0.7 unit per cubic centimeter the antral flora became gram-negative.

The patients showing anaerobic bacterial flora (7 with microaerophylic streptococci, 2 with unclassified anaerobes, 1 with anaerobic gram-negative rods) showed in general a poor response to aerosol treatment given once daily. All 6 such patients that had ephedrine control treatment showed no improvement; of these, 4 were subsequently given penicillin aerosol and 2 improved. Three other patients were treated with penicillin and 1 with streptomycin, without significant improvement. One patient with an anaerobic infection, who showed no change on a full course of penicillin aerosol followed by six antral irrigations, was cured by a right maxillary antrostomy, and has remained completely asymptomatic and clinically free of disease after an eight months' follow-up. In another similar case the patient, who had received a full course of penicillin aerosol with no improvement, was cured clinically by seventeen antral irrigations over a period of five weeks and has likewise remained free of disease after a one month follow-up.

Patients That Received Both Penicillin and Ephedrine Treatment: A group of 10 patients, who are included in the series already presented, afforded an opportunity to serve as their own controls, since all 10 patients were treated with ephedrine aerosol with no improvement and were then given penicillin aerosol. With the latter treatment, there were also therapeutic failures with penicillin in 5 of the 10 cases. Four patients showed moderate over-all improvement with penicillin as compared with ephedrine and 1 patient showed decided improvement with penicllin.

II. Allergic Patients.—The number of patients with predominantly allergice factors was too small to permit comparison between the penicillin-treated and ephedrine-treated patients (table 2). Nine out of 12 patients showed pansinusitis, and 8 had a history of previous polypectomies. As a rule, symptomatic relief was obtained as in the nonallergic patients and was enhanced by the use of oral antihistaminics. In some instances improvement on physical examination could be found, but there were equally few or no changes in roentgenograms, antral contents or bacteriologic observations in both series (table 4).

III. Streptomycin Therapy.—A group of 10 patients with complete or predominant gram-negative flora was treated with streptomycin aerosol. The results, classified according to the presence or absence of allergic factors, are shown in table 4. It can be seen that frequency of symptomatic relief tended to be similar to that obtained with ephedrine or penicillin in comparable types of cases. Objective evidence of improvement in physical examination, roentgenograms, antral contents or bacteriologic studies was slight. Of 7 patients studied bacteriologically before and after treatment, 4 showed disappearance of the original gram-negative organisms at the end of treatment, but at this time 5 patients showed the presence of some gram-negative bacteria in the antrums. In 1 case, Escherichia coli, which at the start of treatment was sensitive to 0.6 microgram of streptomycin per cubic centimeter, showed resistance to 10 micrograms per cubic centimeter at the end of fifteen treatments. In another case E. coli was obtained at the end of treatment which was resistant to 100 micrograms of streptomycin per cubic centimeter.

IV. Follow-Up.—In 20 of the penicillin-treated patients, follow-up observations were made within the first month after treatment. Ten of these patients maintained the moderate or decided improvement they had made during therapy. Seven patients (a third of the total) showed recurrence of symptoms during this time; of these 2 had good over-all results, 3 had moderate improvement and 2 poor results at the end of their courses of treatment. Three patients, all with poor results, were referred for other forms of treatment. Because of the relatively short time the study was in progress, late follow-ups (four to eight months post-treatment, including the winter season) could be obtained in only 6 penicillin-treated patients. The disease in all of these was severe, averaging ten years in duration. Although 4 of these patients had flare-ups in symptoms sometime during this period, they all responded to further courses of penicillin aerosol therapy.

Of the 18 ephedrine-treated patients seen during the first month after treatment, 2 maintained improvement, 6 had recurrences and 10 showed poor results and were given penicillin aerosol.

Similar frequency of recurrences was noted in the small number of patients comprising the allergic groups and streptomycin-treated patients.

V. Reactions.—Of the 23 nonallergic and 5 allergic patients who received penicillin aerosol, 3 showed reactions that were severe enough to warrant cessation of treatment. One patient had a fever, pruritus and generalized erythema after nine treatments, and another had headache, chills and urticaria after thirteen treatments. Both these reactions subsided three days after discontinuation of penicillin aerosol and administration of tripelennamine hydrochloride (pyribenzamine hydrochloride®), 50 mg. four times daily. A patient with previous acute glomerulonephritis, who was receiving his second course of penicillin aerosol treatment for hemolytic streptococcus sinusitis, experienced severe myositis and fever. This case, which was studied at the Presbyterian Hospital and is believed to represent an unusual reaction to penicillin, will be the subject of a future report.[10] An additional patient who previously had had repeated oral penicillin aerosol inhalations for bronchiectasis, during which a sore red tongue had developed, had to discontinue treatments after five days because of the onset of this condition.[11b]

There were no complaints of local irritation of the nose or throat due to penicillin aerosol. Several patients had a brownish coating of the dorsum of the tongue while receiving penicillin aerosol. This was asymptomatic but persisted for several weeks after cessation of treatment.

Most of the patients receiving streptomycin complained of severe nasal irritation and coryza, but no systemic toxicity was noted. One patient with associated bronchial asthma had an exacerbation of this condition throughout her course of streptomycin therapy (eighteen days). The asthma subsided three days after treatment was discontinued. No local or systemic symptoms from ephedrine administration were seen.

COMMENT

It is recognized that corrective surgical procedures of obstructions to drainage from the sinuses, necessary to the proper application of aerosol therapy in some of our cases, in themselves caused some of the improvement noted in both penicillin-treated and ephedrine-treated patients. In like manner, a certain amount of therapeutic credit is due to the power of suggestion of the aerosol apparatus over some patients with psychosomatic components of the disease. Inactivated penicillin was used in those ephedrine control cases with an obvious functional element in an attempt to minimize the suggestive effect of the antibiotic.

Symptomatic improvement of sinusitis during treatment in the cases studied apparently does not depend on the administration of penicillin, but is the result of the improved ventilation and drainage of the sinuses which both methods of treatment provided. The decrease of cough and expectoration seen in cases of sinusitis with associated bronchopulmonary infection can be attributed to the topical application of penicillin aerosol in the lungs during treatment. With equal conditions of sinus drainage, the decided improvement of the physical appearance of the nose and transillumination of the sinuses in the penicillin series suggests that penicillin is the responsible agent. The small number of cases in both categories in which there was complete or partial roentgenographic resolution was not entirely unexpected in this group of patients with chronic disease, a number of whom had had repeated sinus operations and many of whom had had sinus disease for ten or more years. However, the figures show a tendency toward more favorable results in the patients that received penicilin aerosol. Better results were also obtained in the penicillin-treated patients showing fluid broken down pus in the antrums, indicative of a severe degree of infection; however, no significant differences in change of antral contents were noted between the two series when considered as a whole. The bacteriologic changes observed in the penicillin-treated group are thought to be the result of the local bacteriostatic or bactericidal action of penicillin within the paranasal sinuses.

Burtoff,[11] using one or two weekly antral irrigations with daily instillation of penicillin in solution into the antrums in cases of chronic maxillary sinusitis, observed no clinical difference in the results of treatment with saline solutions or penicillin. The use of penicillin, however, resulted in sterile antral cultures after the third or fourth irrigation.

The therapeutic action of ephedrine aerosol and negative pressure is evident in the control cases in which there was improvement. Although it is appreciated that this is a small group, the addition of penicillin to the treatment, in cases of infection with penicillin-sensitive organisms, appears to result in an enhancement of the therapeutic effect. Further suggestive evidence that penicillin aerosol is superior to ephedrine aerosol alone is provided by the results in the 10 patients who served as their own controls.

The response of cases of allergic sinusitis to either ephedrine or ephedrine-penicillin treatment is not pronounced. The swollen state of the allergic nasal and sinus mucous membrane, together with its tendency to develop polypoid degeneration, constitutes a barrier to the ventilation and drainage of the sinuses and to the entrance of penicillin aerosol.

Streptomycin aerosol treatment of chronic sinusitis due to infection with gram-negative bacteria has its

10. Fisk, S. C., and Curran, G. L.: To be published.

11. Burtoff, S.: Evaluation of Diagnostic Methods Used in Cases of Maxillary Sinusitis, with a Comparative Study of Recent Therapeutic Agents Employed Locally, Arch. Otolaryng. **45**: 516-542 (May) 1947.

limitations in that such organisms are prone to become resistant to the antibiotic in a relatively short time. With such time limitations, intensive treatment several times daily seems indicated; however, the local irritative properties of streptomycin may limit the frequency of administration. Doses of 0.2 or 0.3 Gm. three or four times a day may be better tolerated than those used in this study. That in isolated cases this treatment is successful is shown in 2 of our patients with mixed gram-positive and gram-negative infection, who after treatment with penicillin aerosol still showed lack of improvement and the presence of gram-negative organisms in the antrums, which were subsequently eradicated by streptomycin therapy.

In order to obtain optimal results with antibiotic aerosol therapy, it is recommended that antral cultures and antibiotic sensitivity tests of organisms be made prior to institution of treatment and that the appropriate antibiotic be selected as was done in this series. When direct antral cultures are not feasible, nasal cultures of the purulent overflow from the sinuses should be taken.

Although the results obtained with penicillin aerosol tended to be better than with ephedrine aerosol, the over-all effect of penicillin aerosol therapy, as used in these clinic patients with chronic sinusitis, does not justify enthusiasm for the single treatment per day method. Only 3 out of the entire penicillin-treated group showed decided improvement in all five categories studied and 2 of these 3 patients had a recurrence of symptoms and signs two months after cessation of therapy. In considering the penicillin-treated group as a whole, it is noted that a high percentage of recurrences was evident even after a brief follow-up period. It should be noted also that 7 of the 23 patients treated with penicillin aerosol showed little or no improvement in their disease.

In the present series the most gratifying subjective and objective results were obtained in those patients with severe long-standing chronic purulent sinusitis presenting a history of multiple nose and sinus operations and irrigations with little or no relief of symptoms. These patients, almost without exception, did exceedingly well while receiving penicillin aerosol, but recurrence of symptoms after cessation of treatment was the general rule. These flare-ups responded satisfactorily to subsequent courses of penicillin aerosol with negative pressure. Many of these patients reported that this therapy gave them more relief than they had been afforded by any other form of treatment. A number of children were treated successfully, and it was felt that the method was of definite value in the treatment of sinusitis in children, as the use of the apparatus was learned rapidly, and the treatments were taken without resistance or fear of pain on the part of the patient. The same considerations held true in the cases of the adults who were unable to tolerate sinus irrigations. Another group of patients that did well was the one with concomitant chronic sinus infection and chronic pulmonary disease, for the penicillin aerosol had a simultaneous beneficial effect on both processes.

In comparison of the relative merits of antibiotic aerosol therapy in the ordinary case of chronic purulent sinusitis with other forms of treatment of this disease (nasal shrinkage and suction, sinus irrigations, Proetz displacement therapy and the building up of general body nutrition and resistance) it was the clinical impression of the investigator (W. M. G.) with previous experience in these methods that penicillin aerosol–negative pressure treatment alone, given once daily, was not superior to the accepted forms of treatment. Better results may be expected with three or four daily treatments. It was felt further that biweekly or triweekly irrigations of the infected sinus or sinuses gave a more rapid response than did a single daily treatment with penicillin aerosol. Although in this study no series of patients was treated with other methods, good results were obtained with antral irrigation and surgical treatment in isolated cases of severe anaerobic maxillary sinusitis in which there had been no improvement from penicillin aerosol therapy.

In the ordinary case of chronic purulent sinusitis, it is thought that optimal results with this method may be obtained when it is used several times a day in conjunction with periodic irrigations of the appropriate sinuses. In this way the purulent sinus contents would be evacuated, thus making possible direct application of the antibiotic aerosol to the diseased mucosa. Repeated sinus irrigations at intervals of about a week would serve to keep the mucosa exposed to the action of the aerosol. By using this method in conjunction with penicillin aerosol treatments taken at home three or four times daily, one might reduce the frequency of sinus irrigations and achieve quicker control of the infection. Dosage of 100,000 units of crystalline penicillin in 1 cc. of 1 per cent ephedrine sulfate in saline solution or 0.25 per cent phenylephrine hydrochloride (neo-synephrine hydrochloride®), followed by two 0.5 cc. distilled water rinses, is suggested. A study of this method of treatment is contemplated at present.

It is emphasized that competent otolaryngologic appraisal and pretreatment surgical correction of any mechanical blockage of sinus ostiums are absolute prerequisites to the intelligent application of aerosol-negative pressure therapy.

SUMMARY AND CONCLUSIONS

The results in 68 cases of chronic purulent sinusitis with aerosol–negative pressure therapy once daily with and without antibiotics are presented. Comparison of results in 46 nonallergic patients—23 treated with penicillin-ephedrine aerosol and negative pressure and 23 treated similarly without penicillin—provides suggestive evidence that the antibiotic enhances the therapeutic effect. In 12 patients with chronic sinusitis with predominantly allergic factors there was no significant improvement from treatment by the methods described. Ten patients with chronic sinusitis infection due to gram-negative organisms treated with streptomycin aerosol showed in general a poor therapeutic response.

Clinical impressions as to the relative value of penicillin aerosol with negative pressure given once per day as compared with the usual methods of treatment of chronic purulent sinusitis are presented and indications for this type of therapy are suggested. In the ordinary case of chronic purulent sinusitis, antibiotic aerosol therapy given once daily appears to have no superiority over accepted methods of treatment of sinusitis. This method is suggested, however, as a treatment of choice in cases of long-standing chronic disease in patients who have had repeated sinus irrigations and/or extensive sinus surgical treatment with poor response, children and adults who do not tolerate sinus irrigations and in patients with associated chronic bronchopulmonary disease. It is felt that optimal results with this method of therapy would be obtained by combination of multiple daily aerosol–negative pressure treatments with weekly sinus irrigations.

EXPERIENCES WITH NITROGEN MUSTARD THERAPY

C. C. SHULLENBERGER, M.D.
CHARLES H. WATKINS, M.D.
and
ROBERT R. KIERLAND, M.D.
Rochester, Minn.

Until recently, the palliative treatment of lymphoblastoma and other neoplastic diseases has depended almost entirely on the use of irradiation by roentgen rays or radium. With the recent introduction of the nitrogen mustards as potential therapeutic agents in this field, a concentrated effort has been made by various groups of investigators [1] to determine whether there are any specific indications for the use of these substances in place of, or as an adjunct to, irradiation therapy. Since it appears that the biologic effects of the nitrogen mustards and the qualitative clinical response caused by them are similar to, if not identical with, those exerted by irradiation,[2] and since their availability and ease of administration confer definite advantages over irradiation therapy, it becomes a matter of some importance to know what may be expected of these agents when they are employed under certain clinical conditions.

Two fundamental questions are raised. First, is there any advantage to the patient in the use of nitrogen mustard instead of irradiation? An answer to this question can be provided only by comparing, over a protracted period, the results obtained by the administration of nitrogen mustard alone with those obtained by the use of irradiation alone in a similar group of cases. Second, in cases in which the patients have failed to respond or have become refractory to irradiation, is there reasonable hope that nitrogen mustard can still effect clinical remissions? It is the primary purpose of this report to attempt to answer this latter question by an analysis of the results of nitrogen mustard therapy in certain cases in which the patients have been observed at the Mayo Clinic in the sixteen months prior to writing. We are not in a position to provide an answer to the first question, since our experience with regard to the lymphoblastomas has largely been limited to cases in which the disease had been present for a long time and had been treated extensively by irradiation and in which a greater or lesser degree of resistance to irradiation had developed. Secondary objectives of this report will be to present data on nitrogen mustard therapy in diseases other than lymphoblastoma and to call attention to some untoward reactions to this agent.

For a consideration of the fundamental nature of the nitrogen mustards and their mode of action, the reader is referred to the report of Gilman and Philips.[2b] The immediate toxic effects of these agents and their effect on the hemopoietic and other tissues have been described by Gilman and Philips [2b] and by Jacobson and others.[1b] The immediate toxic effects of the administration of these agents, notably nausea and vomiting, do not seem to be a matter of much concern, since they are transient and often tend to decrease in severity during the course of treatment. However, the profound effects of nitrogen mustard on the hemopoietic tissues may result in anemia, leukopenia or thrombocytopenia of severe degree. This makes it mandatory that the physician employing these agents warn the patient of this hazard, that he follow the blood cell counts carefully for at least four to five weeks after therapy has been discontinued and that he be prepared to treat severe leukopenia or thrombopenia should such serious complications arise.

METHOD OF TREATMENT

The nitrogen mustard employed in all of the cases which form the basis of this report was methyl-bis (β-chloroethyl) amine hydrochloride. With few exceptions, a course of treatment consisted of intravenous injections, on four consecutive days, of 0.1 mg. of this material per kilogram of body weight. The total dose for any course, therefore, was 0.4 mg. per kilogram of body weight. In a few cases, it was necessary, because of excessive nausea and vomiting, to lengthen the interval between injections or to terminate the treatment after two or three injections, instead of the usual four, had been administered. It has been our experience that 150 to 200 mg. of pyridoxine hydrochloride, given intravenously at the time of the injection of the nitrogen mustard, often will reduce the severity of the nausea and vomiting which so frequently follow the administration of the latter. As a general rule, we have permitted six weeks to elapse between any two courses of nitrogen mustard, although, in a few instances in which more intensive treatment was indicated and the blood cell counts were satisfactory, we have given a second course between four and six weeks after the first.

In some of our cases of Hodgkin's disease and lymphosarcoma, because of a lack of response to nitrogen mustard, it seemed expedient to return to the use of roentgen therapy alone or to combine the two forms of treatment. In no case, however, did we return to roentgen therapy or to the combined treatment after the administration of nitrogen mustard was begun, unless it became apparent that the use of nitrogen mustard alone had failed to produce and maintain improvement. By proceeding on this basis, it seemed unlikely that any confusion would arise as to which agent was responsible for any effects noted.

RESULTS OF TREATMENT

In attempting to evaluate the effect of therapy on lymphoblastomas and other neoplastic diseases, it seems justifiable that one base judgment only on whether or not the agent employed significantly altered the fundamental lesions and prolonged the life of the patient, in relative comfort, to an extent significantly beyond what one might expect had the agent not been used. In some cases of Hodgkin's disease and lymphosarcoma, the disease runs a surprisingly indolent and protracted course, while in other cases, in which the histologic changes are essentially the same, the disease progresses much more rapidly. This variation makes the evaluation of therapy difficult. One, therefore, should be reasonably conservative in evaluating the results of treatment of this disease.

Fellow in Medicine (Dr. Shullenberger), from the Division of Medicine (Dr. Watkins) and from the Section on Dermatology and Syphilology (Dr. Kierland), Mayo Clinic, Rochester, Minn.

1. (*a*) Goodman, L. S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A., and McLennan, M. T.: Nitrogen Mustard Therapy, J. A. M. A. **132**: 126-132 (Sept. 21) 1946. (*b*) Jacobson, L. O.; Spurr, C. L.; Barron, E. S. G.; Smith, T.; Lushbaugh, C., and Dick, G. F.: Nitrogen Mustard Therapy, J. A. M. A. **132**: 263-271 (Oct. 5) 1946. (*c*) Wintrobe, M. M.; Huguley, C. M., Jr.; McLennan, M. T., and Lima, L. P. deC.: Nitrogen Mustard as a Therapeutic Agent for Hodgkin's Disease, Lymphosarcoma and Leukemia, Ann. Int. Med. **27**: 529-540 (Oct.) 1947.

2. (*a*) Goodman et al.[3a] (*b*) Gilman, A., and Philips, F. S.: Biologic Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides, Science **103**: 409-415 (April 5) 1946.

The subjective improvement which victims of these diseases note as a result of nitrogen mustard therapy, even after the lesions have become refractory to irradiation, is often pronounced. Diminution or disappearance of fever, increase in appetite and strength and decrease or absence of pruritus, for varying periods, are the rule, particularly after the first one or two courses. Yet, in our experience, these primarily subjective signs of improvement may be out of proportion to the strictly objective evidences of improvement, such as decrease in size of the lymph nodes or spleen, shrinking of pulmonary lesions, resorption of pleural fluid or regression of skeletal lesions. The true therapeutic efficacy of any agent is reflected in its ability to, at best, cause regression or resolution of existing lesions, or, at least, to prevent progression of the disease during the period of its utilization. For these reasons, we do not stress, in this report, the transient subjective indications of improvement; rather, we have sought to evaluate the results of therapy on the basis of objective changes in the lesions, the presence or absence of evidences of progression of the disease during treatment and the mortality rate during the period of observation.

TABLE 1.—*Results of Therapy in 18 Cases of Advanced Hodgkin's Disease*

Case	Duration, Mo.*	Period of Observation, Mo.†	Courses ‡	Behavior of Lesions During Period of Observation: Regression of Lesions	Progression of Lesions	Development of New Lesions	Clinical Result
1	36	2	1 NM	+	—	+	Died of unrelated disease. Necropsy showed new progressing lesions
2	24	10	3 NM, 1 RT, 1 NM and RT	—	+	+	Patient's condition deteriorated
3	16	4	2 NM	—	+	—	Died of progression of disease
4	72	5	2 NM	—	+	+	Died of progression of disease
5	132	6	2 NM	±§	—	—	Condition essentially unchanged
6	22	9.5	3 NM, 2 RT	+	—	+	Died of progression of disease
7	42	13	5 NM, 1 RT	—	+	+	Patient's condition deteriorated
8	45	6	4 NM	—	+	—	Patient's condition deteriorated
9	13	4.5	2 NM	—	+	—	Died of progression of disease
10	27	3	2 NM	—	+	—	Died of progression of disease
11	24	3	1 NM, 1 RT	—	+	—	Died of progression of disease
12	29	6	3 NM	±§	+	—	Patient's condition deteriorated
13	36	3	1 NM	—	+	—	Died of progression of disease
14	27	6	2 NM	±§	—	—	Condition essentially unchanged
15	67	4	1 NM	—	—	—	Condition essentially unchanged
16	36	9	1 NM	±§	+	—	Died after pneumonectomy for progressive pulmonary lymphoma
17	23	3	1 NM	—	+	—	Died of progression of disease
18	94	12	2 NM, 2 NM and RT	±§	—	—	Condition essentially unchanged

* Before administration of nitrogen mustard.
† After the administration of nitrogen mustard was begun.
‡ NM denotes nitrogen mustard; RT denotes roentgen therapy.
§ Some of the lesions regressed, while others were unaffected or progressed. In case 16 there was a complete remission of lesions of the superficial lymph nodes for nine months, but the pulmonary lesion continued to progress.

Hodgkin's Disease.—The results of nitrogen mustard therapy, alone or in combination with irradiation therapy, in 18 cases of advanced Hodgkin's disease are summarized in table 1. In each of these cases, microscopic examination of a specimen of a lesion disclosed "lymphosarcoma, Hodgkin's type." All of the 18 patients previously had been treated repeatedly with roentgen rays, and the majority of the patients had noticed that their favorable response to this type of therapy had become less pronounced with each succeeding series of treatments.

In 14 of these cases either the patients died of progression of the disease or their physical condition deteriorated clinically during the period of observation after the institution of nitrogen mustard therapy. In cases 1 and 16, the death of the patients was not directly attributable to Hodgkin's disease but the disease obviously had progressed by the time death occurred. In this group of 14 cases, the duration of the disease prior to institution of nitrogen mustard therapy ranged from 13 to 72 months and averaged 31.8 months. In 5 of these cases, new lesions developed during the period of observation. The time that elapsed between the institution of nitrogen mustard therapy and the development of the new lesions ranged from 2 to 12 months and averaged 9 months. In 12 of the 14 cases, some or all of the original lesions showed clinical evidence of progression within 1 to 5.5 months after institution of nitrogen mustard therapy, the average being 2 months. In the 8 cases in which the patients died of progression of the disease, the duration of life after the institution of nitrogen mustard therapy ranged from 3 to 9.5 months and averaged 4.3 months.

In 4 cases, the clinical condition of the patients at the end of the period of observation apparently was the same as it had been when the administration of nitrogen mustard was started. In this group, the duration of the disease prior to the institution of nitrogen mustard therapy ranged from 27 to 132 months and averaged 80 months.

In the 18 cases of Hodgkin's disease, the lesions which showed measurable regression in response to nitrogen mustard, or to combined nitrogen mustard and irradiation therapy, were almost entirely confined to the lymph nodes and spleen. Lesions of other organs showed little or no response. In 6 of the 7 cases in which pulmonary lesions were present, the therapy had no effect on these lesions, but in the remaining case a combination of nitrogen mustard and roentgen therapy produced moderate improvement in extensive

pulmonary lesions after two previous courses of nitrogen mustard alone had been without effect. At the end of fifteen weeks these lesions again progressed and did not respond to further therapy of the combined type.

The skeleton was involved in 3 cases. Regression of the lesions did not occur in any of these cases as a result of therapy. In 2 of these cases, the lesions progressed during the period of observation.

There was clinical evidence of involvement of the liver in 2 cases. The therapy did not produce any improvement in 1 of these cases. In the other case, the first course of nitrogen mustard produced a significant decrease in the size of the liver, which lasted for six weeks. The enlargement recurred at the end of this period and was not relieved by subsequent courses of nitrogen mustard.

In 6 cases, the erythrocyte count was less than 3,500,000 per cubic millimeter of blood. Leukopenia was present in 2 cases in which the anemia was severe. In these cases, the leukocyte count was less than 2,800 per cubic millimeter of blood. Nitrogen mustard, administered alone or in combination with roentgen rays, did not produce any significant improvement in the anemia or leukopenia in any of these cases. Blood transfusions also were used in some cases, but they likewise did not produce any improvement.

Lymphosarcoma.—Table 2 shows the results of nitrogen mustard in 10 cases of lymphosarcoma. The duration of the disease prior to the institution of nitrogen mustard therapy ranged from 4 to 52 months and averaged 17.6 months. In 6 cases, death occurred from progression of the disease. In these cases, the duration of life after the institution of nitrogen mustard therapy ranged from 1 to 6 months and averaged 3.5 months.

In case 21, the response to nitrogen mustard therapy was more rapid and more complete than it was in any of the other cases of lymphosarcoma. The patient had not been treated previously. Evidence of enlargement of the lymph nodes, spleen and liver disappeared within one week after the administration of nitrogen mustard was begun. The clinical remission lasted for 2.5 months. Enlargement of the spleen and of some of the lymph nodes recurred at the end of this period. In case 24, evaluation of therapy was based on symptoms alone, as the disease was confined to retroperitoneal lymph nodes. There were no physical observations, and the diagnosis was established by laparotomy and biopsy. Abdominal pain of incapacitating degree was the only symptom. This was relieved completely for 4.5 months by the initial course of nitrogen mustard. The pain recurred at the end of this period.

In case 25, enlargement of the spleen and enlargement of the liver were the principal physical observations. Remission could not be considered complete because, despite a decided decrease in the size of these organs as a result of therapy, their size still did not approach normal. Enlargement recurred at the end of six months. In this case, partial remission is to be compared with a partial remission of similar degree which lasted twelve months and was produced by the initial therapy, which consisted of a series of applications of roentgen rays.

Mycosis Fungoides.—Our initial experience with nitrogen mustard in the treatment of mycosis fungoides at the Mayo Clinic has been reported previously.[3] Since the publication of this report, several other patients with mycosis fungoides have been treated. Our knowledge of the value of nitrogen mustard in this disease, however, has not increased to the point where new or more definite conclusions are warranted. The following statements may be made, on the basis of our experience to date. When lesions of mycosis fungoides respond favorably to nitrogen mustard, the effect is apparently identical with that of roentgen rays. The effectiveness of nitrogen mustard therapy tends to diminish with repeated courses. In this disease, development of resistance to roentgen therapy constitutes an indication for a trial of nitrogen mustard, for two reasons. First, further remissions sometimes can be produced by nitrogen mustard. Second, sensitivity of the lesions to roentgen rays may return after the patient has been treated for weeks or months with nitrogen mustard. By thus alternating the two forms of therapy, it is sometimes possible to maintain the patient in relative comfort for a period considerably longer than would be possible by using roentgen rays

TABLE 2.—*Results of Therapy in 10 Cases of Lymphosarcoma*

Case	Duration, Mo.*	Histologic Diagnosis	Previous Roentgen Therapy	Response to Therapy †			Period of Observation, Mo.‡	Clinical Result
				First Course	Second Course	Third Course		
19	6	Lymphosarcoma	+	None	.....	.....	1	Died of progression of disease
20	6	Reticulum cell lymphosarcoma	+	None	.....	.....	3	Died of progression of disease
21	6	Lymphosarcoma	—	Complete remission for 2.5 mo.	.....	.....	4	Patient did not return for further treatment
22	4	Reticulum cell lymphosarcoma	+	None	None (roentgen therapy)	None (roentgen therapy)	5.5	Died of progression of disease
23	13	Reticulum cell lymphosarcoma	+	None	.....	.....	3	Died of progression of disease
24	27	Lymphosarcoma	+	Complete remission for 4.5 mo.	Unknown	.....	4.5	
25	13	Lymphosarcoma §	+	Partial remission for 6 mo.	Unknown	.....	7	
26	37	Lymphosarcoma	+	None	.....	.....	6	Died of progression of disease
27	52	Lymphosarcoma	+	Partial remission for 1 mo.	None	None	6	Patient's condition essentially unchanged
28	12	Lymphosarcoma §	—	None	None	.....	2.5	Died of progression of disease

* Before administration of nitrogen mustard.
† Therapy consisted of 1 course of nitrogen mustard unless otherwise indicated.
‡ After administration of nitrogen mustard was begun. § Diagnosis made by examination of bone marrow.

3. Kierland, R. R.; Watkins, C. H., and Shullenberger, C. C.: The Use of Nitrogen Mustard in the Treatment of Mycosis Fungoides, J. Invest. Dermat. 9: 195-201 (Oct.) 1947.

alone. Microscopic examination of lesions of mycosis fungoides before and after the use of nitrogen mustard reveals that the number of cells constituting the infiltrate in these lesions may be diminished as a result of this therapy, but the histologic picture of mycosis fungoides is still evident in the specimens obtained after treatment. More work of this kind should be done.

Cutaneous Lymphoblastoma.—We have treated 1 patient, a woman aged 41 years, who had suffered for a year from two erythematous infiltrating lesions of the skin of the face, associated with severe pruritus. A specimen of one of the lesions was examined microscopically three months after the onset, and the histologic picture was characteristic of lymphoblastoma. The patient exhibited no other evidences of lymphoblastoma. Two courses of roentgen therapy failed to prevent progression in the size of the lesions. A course of nitrogen mustard was then given. This promptly relieved the pruritus and caused the lesions to regress completely in the next three months. Follow-up data, which were obtained at the end of five months, revealed that the patient was entirely well and had not had any recurrence.

Leukemic Reticuloendotheliosis.—Two patients who had leukemic reticuloendotheliosis were treated with nitrogen mustard. One of these, a man aged 59 years, died twenty-five days after the completion of the therapy. A clinical picture of granulocytopenia developed before the patient died. The other patient was a man aged 75 years who had had severe cutaneous manifestations of reticuloendotheliosis for three years. The blood picture was characteristic. The patient had not had any previous roentgen therapy, and he was not benefited in any way by a course of nitrogen mustard.

Malignant Neoplasms.—In 7 cases of malignant neoplasms of various types, nitrogen mustard therapy was used because all other therapeutic measures were deemed impossible or inadvisable. The clinical data in these cases are summarized in table 3.

Polycythemia Vera.—The obviously profound effect which nitrogen mustard exerts on the bone marrow naturally suggests its use in the attempt to control polycythemia vera. Jacobson and others [1b] have reported remissions lasting up to 12 months as a result of nitrogen mustard therapy. Despite some excellent results which have been obtained in the treatment of this disease with radiophosphorus, Hall and one of us (C. H. W.) [4] have expressed the opinion that the incidence of acute leukemia among the patients treated with this agent may be disturbingly high. This constitutes another reason for evaluation of the therapeutic potentiality of nitrogen mustard in this disease.

To date, we have employed nitrogen mustard therapy in 8 cases of polycythemia vera. A protracted follow-up period will be necessary before the results of this therapy can be evaluated and compared with those obtained with other methods of treatment. At this time, our experience may be summarized as follows: One patient obtained complete symptomatic and hematologic remission for 13 months after one course of nitrogen mustard. Three other patients have reported normal blood cell counts and absence of symptoms between 2 and 3 months after the initial courses. Two patients have reported hematologic and symptomatic relapses between 2 and 3 months after their initial therapy, and 1 of them has received a second course. Follow-up data in the other 2 cases are not available at this time.

We believe that the initial results are sufficiently encouraging to warrant further investigation of the usefulness of nitrogen mustard in the treatment of polycythemia vera.

TABLE 3.—*Results of Therapy in 7 Cases of Malignant Neoplasms* *

Case	Site of Tumor	Histologic Diagnosis	Duration †	Courses of Nitrogen Mustard	Response	Period of Observation ‡	Clinical Results
29	Bronchus	Squamous cell carcinoma, grade 4	16 mo.	1	None	6 weeks	Condition of patient deteriorated; carcinoma cells in sputum 6 weeks after treatment
30	Bronchus	Carcinoma cells present in sputum	10 mo.	2	None	6 mo.	Died of progression of disease
31	Breast; metastatic involvement of cervical and supraclavicular lymph nodes	Adenocarcinoma	12 mo.	3	None	6 mo.	Disease progressed
32	Esophagus	Probably adenocarcinoma, grade 4	5 weeks	1	None	2 mo.	Died of progression of disease
33	Bronchus	"High grade carcinoma"	4 mo.	1	Partial relief of obstructive symptoms for 4 weeks	4 mo.	Died of progression of disease
34	Primary site undetermined; metastatic involvement of supraclavicular and inguinal lymph nodes	Adenocarcinoma, grade 4	2 mo.	1	Subsequent use of nitrogen mustard or irradiation (elsewhere) did not produce any improvement	4 mo.	Died of progression of disease
35	Rectovesical space; metastatic involvement of liver, pancreas, lungs and skeletal muscles	Fibrosarcoma	16 mo.	1	None	5 weeks	Died of progression of disease

* In addition to cases of lymphoblastoma. † Before administration of nitrogen mustard.
‡ After administration of nitrogen mustard was begun.

UNTOWARD EFFECTS OF NITROGEN MUSTARD THERAPY

It is apparent that the accepted therapeutic dose of nitrogen mustard, while safe for the large majority of patients, may be severely toxic for some. It must

4. Hall, B. E., and Watkins, C. H.: The Medical Use of Radioactive Isotopes: Radioactive Isotopes in Hematologic Disturbances and Neoplasms, Am. J. M. Sc. 213:621-628 (May) 1947.

become obvious to the physician who employs this agent frequently that the hemopoietic tissues of some patients are unusually sensitive to the action of this drug. Unfortunately, one cannot predict which patients are likely not to tolerate it. Among the patients with Hodgkin's disease whom we have treated were a few who exhibited anemia, leukopenia and thrombopenia prior to the institution of nitrogen mustard therapy. The use of this agent did not have any obviously severe effect on the blood cell counts of these patients. On the other hand, in a few cases in which the patients had normal erythrocyte, leukocyte and thrombocyte counts before nitrogen mustard therapy was begun, suppression of bone marrow activity reached such degree in the second to fourth week after the last injection of nitrogen mustard that neutrophil and thrombocyte counts reached levels at which serious complications may arise.

We have observed a case in which a clinical and hematologic picture of granulocytopenia with associated purpura developed within ten days after the completion of a course of nitrogen mustard therapy. The blood smears did not reveal any neutrophils and only a few thrombocytes were seen. In 2 other cases in which the usual calculated dose of nitrogen mustard was administered, severe thrombopenia, purpura and intrapulmonary bleeding developed in the third week after therapy. In 1 of these cases, clinical evidence of intracerebral bleeding also occurred. While the nature of the diseases for which nitrogen mustard therapy was instituted in these cases was such that the drug could not be unequivocally incriminated as the cause of these complications, the relationship, in time, of its administration to the clinical deterioration was suggestive. It appears that the use of nitrogen mustard carries a risk; therefore, in employing it, the physician should weigh the seriousness of the existing disease against that of the possible complications arising from the therapy and should recognize that the month following the completion of therapy is a potentially dangerous period during which severe neutropenia or thrombopenia may occur.

SUMMARY AND CONCLUSIONS

This paper includes an analysis of the results of nitrogen mustard therapy, or combined nitrogen mustard and irradiation therapy, in 18 cases of advanced Hodgkin's disease. Our experience indicates that, in cases in which the disease has become more or less refractory to roentgen therapy, nitrogen mustard has very limited usefulness as an agent which may produce transient subjective improvement without necessarily altering or significantly delaying the progressive course of the disease. It is apparent that existing lesions may progress or that new lesions may develop within a few weeks to a few months after institution of nitrogen mustard therapy. Very satisfactory regression of some of the lesions in a given case may occur as a result of this therapy, while progression of other lesions is taking place simultaneously. Lesions which involved nonlymphoid organs responded poorly or not at all to this therapy. Our results suggest that the cases in which there was the least tendency to progression during the period of observation were those in which the disease had existed for the longest time prior to the institution of nitrogen mustard therapy.

The results of nitrogen mustard therapy in 10 cases of lymphosarcoma also have been considered. While the over-all results were not encouraging, in our experience they were unpredictable. While 7 of 10 patients either died within six months or were unimproved after this therapy, it appears that some patients may respond very well to it. From our experience, we cannot draw any conclusions as to the correlation between the histologic pattern in a given case of lymphosarcoma and the responsiveness to therapy.

In our hands, nitrogen mustard has been a valuable adjunct to roentgen rays in the treatment of mycosis fungoides, although its usefulness varies in different cases. A very satisfactory result was obtained with nitrogen mustard therapy in a case of cutaneous lymphoblastoma after irradiation had failed to stop progression of the disease.[5] Initial results in the treatment of polycythemia vera with nitrogen mustard have been sufficiently encouraging to warrant further investigation of its usefulness in this disease. Malignant neoplasms have responded very poorly or not at all to nitrogen mustard therapy, in our experience.

Nitrogen mustard is potentially a dangerous drug and is capable of severely damaging the hemopoietic tissues when used in the presently accepted therapeutic doses. Finally, we believe that a true evaluation of the efficacy and reliability of nitrogen mustard in cases of lymphoblastoma can be determined only by employing this agent alone in a series of hitherto untreated patients and comparing the results with those obtained in treating similar patients with irradiation and with a combination of irradiation and nitrogen mustard.

Clinical Notes, Suggestions and New Instruments

DEATH DUE TO PHENOL CONTAINED IN FOILLE®

Report of a Case

THOMAS D. CRONIN, M.D.
and
RAYMOND O. BRAUER, M.D.
Houston, Texas

A 10 year old white boy was accidentally burned early on a Saturday evening when kerosene was thrown on a fire. He sustained first and second degree burns of the face; anterior part of the neck, chest and abdomen as far as the umbilicus; arms, and a 12 by 9 cm. area on the right thigh, or approximately 25 to 30 per cent of the body surface. The results of the rest of the physical examination were essentially negative.

He was taken immediately to the hospital emergency room and given 500 cc. of plasma and morphine sulfate, ⅙ grain (11 mg.).

The burned areas were clean, so that superficial debridement was carried out after he had responded from the initial shock. A pressure dressing was applied, which was saturated with foille® (a preparation containing phenol, Carbisulphoil Company),[1] and he was admitted to the hospital at 10 p. m. Saturday night.

In the original application, about 2,500 cc. of foille® emulsion was applied, and the nurses were instructed to apply it as often as necessary to keep the dressing moist. They were rather diligent in carrying out this order, so that during the two and a half days the patient lived after he had been burned, more than 7,500 cc. of the preparation was used.

His initial blood test showed 5,680,000 red blood cells, 16.0 Gm. (104 per cent) of hemoglobin and 20,000 white blood cells, with 9 per cent lymphocytes and 91 per cent neutrophils.

5. Since preparing this report, we have employed nitrogen mustard in treating another patient with very widespread cutaneous lymphoblastoma, who had had no previous roentgen therapy. Very remarkable clinical and histologic improvement was apparent three months after the completion of the therapy.

1. The contents are given in detail later in the paper.

He was given penicillin, 30,000 units every three hours, and during the next twenty-four hours he received a total of 1,500 cc. of plasma, 2,500 cc. of dextrose in isotonic sodium chloride solution and more than 600 cc. of water orally, for a total fluid intake of 4,600 cc. The urinary output was about 500 cc. He vomited a small amount of greenish fluid five times and a large amount of clear fluid twice. During the rest of the night, he required nothing for pain, was "mentally clear" and slept well, awaking occasionally for water. The respirations remained about 20 and pulse rate 104 to 116.

By Sunday noon his temperature had risen from 102 to 104 F. rectally after a slight chill. He required codeine, ½ grain (33 mg.), at 10 a. m., pantopon® (an opium preparation containing the total opium alkaloids in the form of soluble hydrochlorides), ⅙ grain (11 mg.), at 1 p. m., and pentobarbital sodium at 1:30 p. m., as he had been "crying and screaming." For the next six hours, he was quiet and slept at intervals, but by 10 p. m., Sunday night, he was very restless and crying again. His temperature had dropped to 100.8 F. and his pulse rate to 100. A hemoglobin determination at this time was reported as 13.0 Gm., or 84 per cent.

During the rest of the night, which was the beginning of his second hospital day, he required pentobarbital sodium, 1 grain (65 mg.), twice and pantopon,® ⅙ grain (11 mg.), once. By 4 a. m. he was complaining of severe intermittent abdominal pain and expelled flatus frequently. In spite of all this, the nurses said that he had a fair night and roused little when given his 6 a. m. dose of penicillin.

On Monday morning it was noticed that his abdomen was distended, but it was difficult to make a satisfactory examination because of the burn. The distention was treated with enemas and a rectal tube inserted, with returns of a dark brown liquid and considerable flatus.

His fluid intake during Sunday night and Monday, his second hospital day, was 500 cc. of blood, 1,750 cc. of dextrose, 750 cc. of plasma and over 170 cc. of water, for a twenty-four hour fluid intake of 3,170 cc. This twenty-four hour output was unknown. At 10:30 p. m. Sunday, beginning his second day, it was first noticed that his urine was very dark. After this, he passed three similar specimens, one of which amounted to 240 cc. The final eight hours of this day he put out no urine. He had lost some fluid through the rectal tube and Wangensteen suction apparatus, the latter having been put in place early Monday evening. Shortly after the suction was begun, he was given a sodium bicarbonate enema, with highly colored returns, containing no fecal material.

During this second twenty-four hour period he had repeated blood cell counts. The hemoglobin at 7:30 a. m. was 14.5 Gm. (94 per cent); in the early evening it was 12.5 Gm. (81 per cent), and at 7 p. m. it was 13.0 Gm. (84 per cent). The hematocrit reading in the afternoon was 37 per cent. More complete studies were not done, because of the technical difficulties involved in getting the blood.

We first saw him in consultation on Monday at noon. At this time, he had a cannula tied in the left saphenous vein, the abdomen was distended and he was in a stuporous condition. It was believed wise not to disturb the dressings, but concentrate on giving him the blood and plasma he was then receiving. His lethargy was partially attributed to the pantopon® which he had received forty-five minutes before.

We saw him four hours later, at which time his temperature had risen to 101 F. and he was still stuporous, seemingly out of proportion to the condition to be expected from the burns alone. All treatment with narcotics had been stopped after our first visit. Shortly before this, he became rather cyanotic and nasal oxygen therapy was begun. It was now that it seemed to us that part of the odor of the foille® was that characteristic of phenol.

A pharmacist was called, who stated that foille® contained 2 per cent or more phenol. The dressings were removed and replaced with a petrolatum gauze pressure dressing. It was noticed that all the burned surfaces had a white parchment appearance, with little or no serous oozing from the surface. This dressing change was accomplished without anesthesia and with no resistance from the patient.

Late Monday night and early Tuesday morning (which was the beginning of his third day) his respirations became noisy and labored, with gurgling sounds in the trachea. Suction of the mucus was required to maintain the airway. There were also many moist musical rales. The mucus increased and later became foamy and pink tinged.

During the patient's final seventeen hours his output was 1,100 cc. of dark urine. He lost 240 cc. of a dark brown liquid through the Wangensteen tube. His intake, meanwhile, amounted to 500 cc. of blood, 1,500 cc. of dextrose in isotonic sodium chloride solution and over 75 cc. of water, for a total fluid intake of 2,075 cc.

By early Tuesday morning he was comatose, with grunting irregular respirations; the temperature had increased to 103.4 F. and the pulse rate to 134. His condition remained about the same until about 2 p. m. Tuesday, when the respirations became rather shallow and rapid and his pulse weak. He died at 3:15 p. m.

Postmortem Examination.—Postmortem examination revealed a superficial burn over the areas previously described, with decided edema of the face and neck. The pleural, pericardial and peritoneal cavities were smooth and glistening, with some straw-colored fluid in the pericardial cavity. The lungs showed spotty, firm, dark brown and reddish areas, especially in the lower lobes; microscopic examination showed hypostatic pneumonia. The trachea and bronchi contained mucus, and the mucosal lining was hemorrhagic.

The spleen was grossly normal, but microscopically showed acute congestion. The adrenal glands, heart and aorta were essentially normal. The liver grossly was light brown, firm in consistency and about normal size. On sectioning, the cut surfaces were light brown, but the liver markings were not as clear as normal. Microscopically, it showed a midzonal necrosis, involving almost all the liver lobules with complete destruction of the involved cells.

The kidneys were normal in size. The capsules stripped with ease, revealing pinkish red surfaces. On sectioning, the demarcation line between cortex and medulla was visible. Microscopically, the glomeruli were normal, but the epithelial cells lining the tubules showed decided parenchymatous degeneration with loss of the cellular configuration.

The digestive tract showed acute congestion.

Chemical studies were made by Henry O. Nicholas, Ph.D., Associate Professor of Chemistry, Rice Institute. He reported the following observations: a total volume of urine of 220 cc., a trace of free volatile phenols and 22 mg. of conjugated phenols per hundred cubic centimeters of urine. The total volume of gastric juice was 18 cc., with a trace of free volatile phenols and 18 mg. of conjugated phenols per hundred cubic centimeters of gastric juice. The results of tests of mixed tissues (liver, stomach wall, kidney, qualitative tests only) were strongly positive for both free and volatile phenol. In the analysis of foille® for phenol, one method showed the presence of 1.4 per cent phenol by weight and another method showed the presence of 1.8 per cent phenol by weight.

In reviewing this case, it would seem that the pathologic process was probably already fixed by the time we saw him, as 7,500 cc. of the foille® (105 to 147 Gm. of phenol, depending on whether 1.4 per cent, the lowest figure of Nicholas, or 1.97 per cent, the Carbisulphoil Company figure, is used) had already been applied to the dressings.

The damage to the kidneys was apparent within twenty-four hours of the application of the foille,® as a urine specimen was reported as having a dark color as early as 10:30 p. m. Sunday night. The patient passed three other dark specimens during the following sixteen hours, after which he put out no urine for nine and a half hours. After this period of anuria, the output was greater than it had ever been, almost equaling the intake for this period, when previously the output had always been small compared with the intake.

The initial study of the blood showed hemoconcentration, but later studies did not, as would have been expected if the fatal outcome was due to the burn alone. In our experience, the stuporous condition noted in this patient was out of proportion to the extent of the burn.

OTHER REPORTS

Johnstone [2] reported a case of a 22 year old man who accidentally spilled a bottle of carbolic acid, saturating the "right leg, right side of the abdomen and the chest." Fellow employees immediately removed his shirt and threw water over the upper part of his body. He then walked across the street to a physician's office without difficulty, but collapsed and died within fifteen minutes of his arrival. Autopsy revealed, in addition to the local first and second degree burns, "hyperemia and edema of the lower lobes of both lungs, and marked hyperemia and edema of both kidneys, pancreas and spleen. There was no change in the heart or liver. Analysis of portions of the pancreas, spleen and kidneys was positive for carbolic acid, and the chemist reported the quantity found was increased five times over that usually found in these tissues at autopsy."

Thienes and Haley [3] said, regarding the toxic dose, ". . . 5 grs. of phenol or creosol or 1 cc. creosote may cause dangerous symptoms. Three grams of any one may be fatal although recovery after 150 cc. of creosol has occurred." Gonzales, Vance and Helpen [4] stated, ". . . the fatal dose of phenol is about one-half ounce when it is taken by mouth. . . . When used in wounds or body cavities, a small dose can be quite dangerous. The average duration of the clinical course in a fatal case is from two to twelve hours, but may be shorter or longer."

The symptoms of poisoning are "dizziness, delirium, sometimes convulsions, collapse and loss of consciousness, fall of temperature (or sometimes fever), labored breathing and oliguria with dark urine." [3] The dark urine is an early symptom of mild poisoning. Cases of delayed death show symptoms of renal necrosis—oliguria or anuria, albuminuria, hematuria, edema and retention of waste products in the blood. The odor of phenol is noticeable on the breath.

Phenol is detoxified by the liver after absorption and is excreted by the kidneys as ethereal sulfates, hydroquinol or pyrocatechol, glucuronates and free phenol. A trace is excreted by the lungs. It produces cerebral edema and cardiac dilatation. If life persists for one-half hour or more, there is glomerular and tubular degeneration of the kidneys with central necrosis of the liver.

The diagnosis is made by the histologic picture of the liver and kidneys together with the chemical analyses. "Phenols may be demonstrated in suspected bottles, in stomach washings or in urine. At autopsy the odor may be detected, even before opening the stomach." [3]

The cause of early death is due to shock, respiratory failure or cardiac collapse. Delayed death is of renal or hepatic origin.

In 1941, the Council on Pharmacy and Chemistry [5] reported on foille® at the request of the Carbisulphoil Company of Dallas, Texas. The product was submitted as a "new protective antiseptic and analgesic dressing in the local treatment of recent and infected burns, traumatic and infected wounds and indolent ulcers." It was stated to consist of the following ingredients:

Alcohol	1.20
Phenol	2.36
Benzocaine [ethyl aminobenzoate]	1.26
Calcium soap	0.36
Calcium iodide	0.24
Potassium iodide	0.12
Oxyquinoline base	0.18
Calcium thiosulfate	0.03
Calcium sulfite	0.07
Calcium sulfate	0.13
Sulfur (free)	0.17
Water	2.85
Corn oil (fixed)	90.33
Glycerine	Present

The manufacturer further claimed: "The benzocaine plus the phenol is said to effect an immediate and pronounced anesthesia which mitigates shock and pain to provide a distinctly favorable factor in the initial stage of a serious burn. The action of the soap augmented by phenol on prolonged contact is claimed to coagulate the serum exudation, excluding air and forming a soft shield."

"In support of claims for the product, the manufacturer submitted . . . additional laboratory statements to show that poisoning from the phenol contained in the product will not occur because it is not appreciably absorbed through the skin because of its affinity for the water-in-corn oil vehicle and that a mild antiseptic action occurs with prolonged application."

In summarizing its report, the Council stated, "The evidence submitted by the firm to support the claims for Foille is largely testimonial, poorly, if at all, controlled and consists of considerable reduplication of material. The case reports submitted are further inadequate from the standpoint of blood studies by which to evaluate the systemic condition of the patients." It went on, "Aside from the question of systemic absorption, the possible danger of local injury to tissues by the action of 2.35 per cent phenol should be considered." The Council voted that foille® be "not accepted for inclusion in New and Nonofficial Remedies because it is marketed under an uninformative proprietary name without satisfactory evidence to establish the therapeutic rationale for its complex formula and the claims made for it."

A brochure furnished by the Carbisulphoil Company states, "In the local treatment of major or minor burns and other wounds, Foille may be used not only for first aid but in the further management of the patient. . . . Dressings saturated with Foille emulsion should be applied directly to the wound and the dressing kept moist with Foille. . . . In some cases, depending upon the clinical picture—temperature, pulse and respiration—it may be appropriate to continue with the original dressings for a longer period of time by frequently saturating them with Foille in order to keep the area moist, soft and pliable. Such treatment may be continued either with or without changing the dressings until healing is complete or until conditions are satisfactory for grafting." The formula listed in the brochure was essentially the same as that given previously, except that the total phenol was stated to be less than 1.97 per cent.

COMMENT

In foregoing quotation, it should be noted that the free use of foille® is advised in both major and minor burns and for unlimited periods. Nowhere in the brochure is there any warning as to the possible danger of absorption of phenol.

We believe that the use of phenol in this mixture is dangerous and, furthermore, is irrational, as burned patients are soon fairly comfortable after the application of bland agents, such as petrolatum. Certainly there is no justification for the continued use of phenol on a burned patient.

We have found no reports of fatalities from the use of foille,® but a sober consideration of the events in this case would indicate that there have probably been other deaths due to the contained phenol. It is probable that in these cases the death has been attributed to the burn itself.

We feel that foille® as now constituted, with approximately 1.97 per cent phenol, is a dangerous and irrational preparation which should be withdrawn from the market immediately.

SUMMARY

A case is presented of a 10 year old boy with 25 to 30 per cent of the body surface burned. The clinical course and chemical and postmortem examinations revealed phenol poisoning due to the absorption of phenol contained in foille® (Carbisulphoil Company), the substance applied as the local dressing.

The toxicologic aspect of phenol poisoning is presented. The product foille® was not acceptable to the Council on Pharmacy and Chemistry Aug. 2, 1941. The use of phenol (1.97 per cent) in foille® should be discontinued, as fatal intoxication may result.

2. Johnstone, R. T.: Occupational Medicine and Industrial Hygiene, St. Louis, C. V. Mosby Company, 1948, p. 216.

3. Thienes, C. H., and Haley, T. J.: Clinical Toxicology, Philadelphia, Lea & Febiger 1948, p. 31 and 163.

4. Gonzales, T. A.; Vance, M., and Helpen, M.: Legal Medicine and Toxicology, New York, D. Appleton-Century Company, Inc., 1947 and 1940, p. 485-488.

5. Foille (Carbisulphoil Company) not acceptable for N. N. R., report of Council on Pharmacy and Chemistry, J. A. M. A. **117**: 363-365 (Aug. 2) 1941.

Council on Pharmacy and Chemistry

REPORT TO THE COUNCIL

The Council has authorized publication of the following report.
AUSTIN SMITH, M.D., *Secretary.*

A STATUS REPORT ON ANALEPTICS

JAMES E. ECKENHOFF, M.D.
With the Assistance of
CARL F. SCHMIDT, M.D.
ROBERT D. DRIPPS, M.D.
and
SEYMOUR S. KETY, M.D.
Philadelphia

Although knowledge about the nature of the changes which analeptics[1] produce in cells is almost totally lacking, the drugs now in use as analeptics fall into four convenient categories:

1. Those which have a primary stimulant action on the nervous system and the value of which depends on that action. The representatives of this group are picrotoxin, metrazol® (pentamethylenetetrazol), nikethamide (coramine®), strychnine, caffeine and atropine; the latter three may be regarded as obsolescent or (particularly atropine) obsolete for analeptic purposes.

2. Drugs the analeptic effects of which are due to reflexes from one source or another. The most powerful of such reflexes are those from the carotid and aortic bodies. Alpha lobeline owes its therapeutic action to the stimulation of these structures. Cyanides, sulfides and nicotine are capable of similar actions but are not used because of their extremely toxic properties and connotations. Irritants of the nose, mouth and stomach (smelling salts, aromatic spirits of ammonia, whiskey, brandy) belong in this category, as do subcutaneous injections of camphor, alcohol or ether and any type of chemical or physical intervention capable of arousing sensory impulses which bombard the central nervous system (e. g. slapping, walking).

3. Drugs which stimulate both the central nervous and cardiovascular systems and which, in sufficient dosage, produce not only convulsions but also hypertension and tachycardia. Their analeptic effects presumably depend not only on the direct stimulation of nerve cells (as with group 1), but also an increase in the blood supply to the brain. This group includes practically all of the aromatic sympathomimetic amines, but for this purpose those in which the central nervous stimulant action is relatively great and the sympathomimetic effect relatively small are preferred to those in which the opposite relationship exists. Thus amphetamine (benzedrine®), d-amphetamine (dexedrine®) and desoxyephedrine (methedrine®) are preferable analeptics to epinephrine, paredrine® (*p*-hydroxy-*a* methyl-phenyl-ethylamine) or phenylephrine hydrochloride (neo-synephrine hydrochloride®), with ephedrine in an intermediate position. Alphatic pressor amines, 2-aminoheptane sulfate (tuamine sulfate®) and methylamino-iso-octene (octin hydrochloride®); imidazole pressor derivatives, like naphazoline hydrochloride (privine hydrochloride®), and special agents, like posterior pituitary and ergot derivatives, do not stimulate the central nervous system sufficiently to be useful in this connection.

4. Substances which exert a specific stimulant effect on nerve tissue by entering directly into the biochemical reactions on which the excitability of this tissue depends. These include intermediate products of carbohydrate metabolism, such as pyruvate, succinate and fumarate as well as the components of the vitamin B complex.

Analeptics have not proved to be infallible when used in the treatment of central nervous system depressions. This may mean that the drugs now available for this purpose are deficient in important respects and that intensive search is indicated for other agents which would produce superior clinical results, or it may mean that the available analeptics are capable of doing practically everything that can reasonably be expected of drugs of this type. If the second of these is true, further improvement in the management of the unconscious patient would depend on other measures based on a better knowledge of the underlying derangements.

In an attempt to assess the present status of analeptics a most important consideration becomes an understanding of what such drugs may be expected to accomplish. This amounts to an inquiry into the nature of the changes which underlie unconsciousness or coma, as encountered clinically, and the manner in which analeptics affect these abnormalities. These questions will be considered.

THE CAUSES OF CLINICAL DEPRESSIONS OF THE CENTRAL NERVOUS SYSTEM

The common underlying mechanism in all severe depressions of the central nervous system appears to be an interference with the complex metabolism of nerve tissue. The integrity of this metabolic process depends on at least two conditions. The first of these is the homeostasis of the cellular environment, a term which Cannon used to characterize the maintenance of a constant and optimal concentration of available oxygen and glucose, of carbon dioxide and hydrogen ion and a host of other substances. This homeostasis is achieved only by a well integrated functioning of the cardiovascular, respiratory, assimilative and excretory mechanisms of the organism. In addition to an optimum cellular environment, there must be present, for a normally functioning central nervous system, certain intracellular mechanisms for the proper conversion of energy. These two conditions may serve as a basis for a classification of the relatively acute depressions with which this discussion is concerned. Such a classification is important and even urgent if rational therapy is to be achieved.

CLASSIFICATION OF ACUTE CENTRAL NERVOUS SYSTEM DEPRESSION

A. Failure of homeostasis
   1. Changes in composition of arterial blood
      (*a*) Lack of available oxygen and/or accumulation of carbon dioxide (respiratory disease, depression or cessation)
      (*b*) Lack of available nutrient material (glucose primarily)
   2. Failure in cerebral circulation
      (*a*) General circulatory derangements (heart failure, asystole, decreased blood volume, loss of vasomotor tone—all characterized by a low systemic blood pressure)
      (*b*) Local circulatory disturbances (increased intracranial pressure, cerebral arterial spasm, occlusion or rupture)

From the Department of Anesthesiology, Harrison Department of Surgical Research and Department of Pharmacology, School of Medicine, University of Pennsylvania.

1. An analeptic may be defined as a drug capable of stimulating the normal central nervous system and which is used for the purpose of overcoming a depression of that system.

B. Failure in intracellular metabolism
   1. Lack or destruction of certain intracellular enzyme systems (deficiency diseases, "irreversible" stage of other depressions)
   2. Action of noxious substances
      (*a*) Endogenous—acidosis, ketosis, uremia
      (*b*) Exogenous—narcotic or other drugs

Most clinical depressions involve more than one of the causes listed, either from the start or as subsequent complications. From the point of view of the present discussion, there is little doubt that depressions caused by narcotic drugs are the most amenable to analeptic drugs. Other depressions are less likely to be helped and may indeed be intensified by analeptic therapy, particularly if such therapy is followed by convulsions.

THE MECHANISM OF ANALEPTIC ACTION

Since analeptics are most effective in the presence of a narcotic depression, it is probable that the actions of the two types of drugs are intimately related. The more probable relationships are: (1) direct chemical inactivation or neutralization of the narcotic by the analeptic, (2) diminution in the effective concentration of the narcotic agent within the nerve cell and (3) physiologic antagonism, i. e., increased excitability of nerve cells overshadowing a continuing depressant effect.

There is no evidence that would indicate a direct inactivation of a depressant drug by an analeptic agent, either *in vitro* or *in vivo*. In view of the diverse chemical and physical properties of narcotics and analeptics, it would indeed be surprising if a common reaction were demonstrated.

A rational and simple explanation of the mechanism of action of analeptics would be a diminution in the effective concentration of the depressant in nerve cells brought about by displacement of the narcotic from combination with neuronal protoplasm or by promotion of its excretion or detoxification. The displacement theory is supported by the evidence that picrotoxin stimulates breathing only when respiration is depressed, and then as part of a general awakening from narcosis. These phenomena are, however, peculiar only to certain depressants (phenobarbital with morphine, chlorobutanol, paraldehyde and tribromoethanol solution [solution avertin with amylene hydrate®]) and to picrotoxin as the stimulant; they have not been seen when metrazol, caffeine or nikethamide was used to counteract these same narcotics or when picrotoxin was used against depressions caused by urethane or ethyl alcohol, and, finally, they apparently are seen only in light or moderate depressions but not in deep narcosis.

If the displacement theory is correct, the concentration of narcotic in the cerebral venous blood should rise and that in nervous tissue should fall when the analeptic effect is at its height. There are as yet no data concerning this phase of the problem. Concentrations of paraldehyde, avertin® and barbiturate in *systemic* venous blood have not been significantly altered by the administration of analeptics, but this would not preclude a concomitant mobilization of the narcotic from the brain and deposition in other tissue. The methods for quantitatively estimating the barbiturate content of tissues and blood have been too inaccurate to warrant confidence in the observations, but the recently described spectrophotometric procedure may make possible a definitive answer to this question.

According to the published evidence, physiologic antagonism is the most probable explanation for the reciprocal relationship between analeptics and depressants. In favorable circumstances the antagonism may be so nearly perfect that a mixture of a narcotic and an analeptic can be injected intravenously with surprisingly little effect, although the amount of each agent is such that coma or convulsions would occur if it were given alone. Similarly, a dose of barbiturate which would otherwise be fatal will cause only a depression if given with an analeptic; respiratory failure produced by intracisternal injection of a barbiturate can be counteracted by a similar prompt injection of picrotoxin, and the stupor produced by certain barbiturates may often be instantly terminated by intravenous injection of a suitable analeptic in laboratory animals or in human subjects.

The explanation of this antagonism depends on knowledge of the cause of the narcotic depression, which is still obscure. The older physicochemical conceptions of narcosis, such as the lipid, surface tension and adsorption theories, have ceased to attract attention or stimulate fundamental research, largely because recent discoveries of the complex biochemical relations existing in even the simplest cells have rendered unlikely a simple all-inclusive explanation for all of the observed phenomena of narcosis. One of the recent trends has been a revival of the idea formulated originally by Verworn, viz., the fundamental feature in the narcotic process is interference with oxidative reactions on which cell functions depend. Quastel and his associates were able to show a consistent depression of the uptake of oxygen by nerve tissue in vitro in the presence of concentrations of narcotics within a range compatible with life. In the monkey's brain *in vivo* oxygen consumption was found to be depressed by narcotics and elevated by analeptics, the changes in oxygen uptake showing a close parallelism to the concomitant changes in functional activity. A limited amount of recent evidence indicates that the same parallelism exists in human beings in different physiologic and pathologic states. There are data to indicate that narcotics interfere with the dehydrogenating enzymes rather than those directly concerned with oxygen; this is shown by the fact that under the influence of narcotics cytochrome C can take up oxygen in a normal manner but cannot release it again.

The opposing action of analeptics has not been studied from the point of view of anything but over-all activity or oxygen uptake. Conceivably analeptics might: (1) specifically displace narcotics from their combination with cell dehydrogenases, (2) serve as coenzymes or specific substrates which would permit normal or hypernormal cell oxidations in spite of the narcotic, (3) combine with neuronal protoplasm in some manner unrelated to the narcotic but capable of overpowering its effects or (4) set up nerve impulses sufficiently strong to produce the latter type of result. Choice among these is a matter of individual preference until the underlying mechanisms are better understood.

An interesting variation of this conception of physiologic antagonism has to do with the effects of narcotics and analeptics on synaptic transmission. Dripps and Larrabee have observed that barbiturates will depress this process if used in greater than anesthetic doses and that metrazol® could counteract the depression and cause facilitation. This cannot be made the basis for a general explanation of analeptic action, however,

because picrotoxin does not affect synaptic transmission and nikethamide only depresses it.

From the foregoing discussion, it becomes apparent that the mechanism of action of analeptics has not been clearly elucidated but that current evidence favors the theory of physiologic antagonism. It should be understood that other possible mechanisms of action are excluded only because of the lack of positive evidence. Final clarification of the mechanism of action of analeptics must await some or all of the following: (*a*) development of an acceptable method for quantitative determination of a barbiturate in body fluids, (*b*) the planning and execution of carefully controlled experiments designed to measure the normal deposition and removal of narcotics in tissue and the influence of analeptics on such deposition and removal and (*c*) further information on the mechanism of narcotic depression.

EVALUATION OF INDIVIDUAL ANALEPTIC AGENTS

In evaluating individual analeptics, the following facts must be recognized: (*a*) Patients have recovered from more than usually fatal doses of barbiturate without the benefit of an analeptic; (*b*) there are definite hazards in the use of analeptics for the treatment of depressant states, and (*c*) no analeptic can be depended on to cause the recovery of a patient deeply depressed from a usually fatal dose of a barbiturate.

Much of the difficulty in obtaining significant data for the evaluation of analeptics is due to the wide variability in the response of human beings or animals to the same dose of a barbiturate. The minimum lethal dose of a given barbiturate may vary widely in different groups of the same species of animals or may change in the same group with the season of the year. In patients additional factors play a part in determining this variability. These include: the degree of absorption of a given dose of drug, the presence of coexistent disease, the age and physical status of the patient and the period between ingestion of the drug and onset of treatment. For the evaluation of the effectiveness of analeptics, these factors and others to be elucidated in this report must be taken into consideration. To one examining the literature critically, it becomes apparent that, in spite of the large number of reports, those containing complete or incontrovertible data are relatively few. The outstanding deficiencies of many of the existing reports are: a lack of adequate controls, the fact that conclusions have been drawn on very small numbers of experiments, the inability of one group to duplicate the observations of another and the use of experimental methods which are difficult of interpretation. Another distinct impression is that many investigators have attempted to draw conclusions on the basis of inadequate dosages of the analeptics. The following paragraphs summarize the data that are generally accepted, except for the reservations mentioned, for the use of individual analeptics.

Picrotoxin.—In 1936 and again in 1939, the Council on Pharmacy and Chemistry published reports on the use of picrotoxin as an analeptic agent. These reports cautioned that picrotoxin had not been fully evaluated and should be used only by those fully aware of its potentialities. The laboratory data available today suggest that picrotoxin is the most potent analeptic agent for use in treating barbiturate depression, but the published clinical data do not offer completely convincing proof that this drug is the drug of choice for analeptic use against all narcotics.

The administration of picrotoxin to normal human beings or animals produces practically no effect until the dose is large enough to produce convulsions. Subconvulsive doses do not affect circulation or respiration or elicit other signs of significant central nervous system stimulation. However, if picrotoxin is given to an animal in which the respiration and circulation have first been depressed by a barbiturate, an increased minute volume of respiration and a rise in blood pressure may be noted. These are the result of direct stimulation of the respiratory and vasomotor centers.

This apparent antagonism between picrotoxin and barbituric acid derivatives has been substantiated by experiments such as the following: 1. Linegar and his co-workers administered intravenously alternate doses of barbital sodium and picrotoxin to rabbits and were able in this manner safely to expose their animals to total doses of the barbiturates which were four times the estimated lethal dose. 2. Picrotoxin and narcotic doses of pentobarbital injected simultaneously into a vein in rabbits caused depression for about 10 minutes only. Coriamyrtin, which is chemically and physiologically similar to picrotoxin, when given simultaneously with the same barbiturate actually prevented the rabbit from being depressed at all. The explanation of the difference in action between these two analeptics lies in the latent time of action of picrotoxin, which may be as long as 10 to 30 minutes, a trait distinguishing it from all other analeptics and complicating its proper clinical administration. 3. Another antagonistic effect of narcotics and depressants was shown by the experiments of Maloney and Tatum. Two dogs were simultaneously given lethal doses of amytal® (5-isoamyl-5-ethylbarbituric acid). One of these dogs was then treated with picrotoxin and the other used as a control. When the control dog died the treated dog was killed, and both were examined at necropsy. The lungs of the control dog revealed a complete obliteration of all alveoli, while the treated dog showed only patchy areas of congestion in the lungs. The difference presumably was due to differences in respiratory and circulatory activity, but a greater number of experiments in this series would have been comforting.

Picrotoxin can cause harm to the patient in several ways. First, it may produce convulsions, which have commonly been reported during the picrotoxin therapy of narcosis. The most important reason for these convulsions is the latent period of 10 to 30 minutes between intravenous injection and onset of the full effect of picrotoxin. If the clinician administering the drug does not wait this full interval before giving subsequent doses, convulsions may occur. Usually there are some premonitory signs of convulsions, but there are reports of convulsions appearing without any warning 30 minutes after picrotoxin was administered. In the event of deep depression it is unwise to attempt a complete arousal, since convulsions may appear before awakening. Should convulsions appear, they will certainly lead to a secondary depression and clinically may have led to the loss of life. In profound depressions, picrotoxin should be administered only to the point where reflexes have returned and blood pressure and respiration are maintained.

The second possibility of harm by pictrotoxin is that it may lead to a depression per se. However, most of the laboratory and clinical reports do not substantiate this conclusion unless the analeptic has been given to the point of convulsions following which a secondary

depression has often appeared. One report has appeared in which 2,134 mg. of picrotoxin was used, but a convulsion appeared on the eighth day of treatment which resulted in a secondary depression from which the patient never recovered. Large quantities of picrotoxin have been given to patients with barbiturate poisoning with subsequent recovery without secondary depression (viz., 1,745 and 1,020 mg.).

The duration of action of a single dose of picrotoxin is longer than that of metrazol® or nikethamide, so that in clinical usage the interval between doses should be longest with this drug. Following intravenous administration to dogs and rabbits, 5 mg. per kilogram of body weight leaves the blood so rapidly that in 20 minutes the blood concentration has leveled off and in 2 hours it has become negligible. Apparently all tissues take up the drug, but the exact site of detoxification is unknown. It is known to be detoxified at the rate of 1.5 convulsive doses in 100 minutes in rabbits.

Picrotoxin apparently is not the drug of choice in all depressions. Its relatively delayed action and the consequent difficulty of dose regulation preclude its use in any but deep depressions caused by the barbiturates. It is said to be contraindicated in morphine poisoning, but most of the data have been obtained from animals. Since there are wide species differences in the actions of morphine, data obtained in animal experiments have only limited value in relation to human beings. Picrotoxin has been advocated in poisoning from sodium bromide, but in depressions from other drugs other analeptics have more commonly been recommended.

Metrazol.®—Metrazol® (pentamethylenetetrazol) has generally been found to be a valuable analeptic agent, but according to results of animal experiments it is inferior to picrotoxin in potency. Probably the most important difference between the two drugs is that metrazol® elicits its maximum effect immediately following intravenous injection; the drug is therefore of value in treating the respiratory depression that may follow the intravenous injection of the short-acting or ultra-short-acting barbiturates. Metrazol,® like picrotoxin, has little effect on the respiratory center in the unanesthetized animal, but the stimulating properties on the depressed center have been demonstrated conclusively. There is apparently no remarkable effect on the vasomotor center except when very large doses are injected rapidly. When the drug is injected intravenously there is usually a transient hypotension, probably due to a peripheral vasodilator effect. Richards and Menaker expressed the opinion that metrazol® is more effective on the higher centers than picrotoxin and for this reason have suggested the drug as an adjunct to picrotoxin in profound barbiturate poisoning after the latter drug has maintained the reflexes, blood pressure and respirations without causing arousal. Patients awakened from thiopental sodium anesthesia with intravenously administered metrazol® frequently retch, vomit and become restless, particularly if a large dose of metrazol® has been injected rapidly. One wonders whether patients so aroused from anesthesia are any less a nursing problem than those allowed to "sleep out" their anesthesia.

Although metrazol® acts rapidly, its duration of action is brief and the drug may have to be injected at frequent intervals. There is quick equal distribution in all of the tissues with rapid detoxification, presumably in the liver. Werner and Tatum found that in the rabbit 1.66 convulsant doses were detoxified in 100 minutes. The rapidity with which a patient, awakened from thiopental sodium anesthesia with a single intravenous dose of metrazol,® returns to his former state of coma causes one to suspect that the detoxification rate of rabbits may be slower than in human beings.

Metrazol® has not been uniformly effective against large doses of the longer-acting barbiturates, although some case reports of successful results have appeared. The failure of the drug as an analeptic is too often associated with the use of inadequate initial doses and neglect to repeat as often as needed.

Nikethamide.—All available evidence indicates that nikethamide is definitely inferior to pictrotoxin or metrazol® as an analeptic agent in the treatment of barbiturate and most other depressant states. We are not aware of any comparative study of these three drugs that has claimed superiority for nikethamide. The reports favoring its use are for the most part uncontrolled clinical studies. From this it follows that there is no justification for statements such as "the most useful and reliable drug up to date, particularly where barbiturates are concerned" and "traditional value as an antidote for barbiturate."

There is no indication of a remarkable cerebral stimulant action of nikethamide in a barbitalized animal, and there are numerous reports of a secondary depression without convulsions following the use of the drug. In a number of conrolled experiments in which nikethamide was used to treat a central depression, the incidence of deaths was higher in the treated group than in the controlled group.

Various other unwarranted claims have been made for this drug: 1. It consistently leads to an elevation of blood pressure, a claim apparently based on experiments with rabbits but apparently not true in some other commonly used laboratory animals. Gunther and his associates and Schube were unable to demonstrate more than occasional elevations in blood pressure in normal or in hypotensive patients. 2. The drug has been considered a cardiac tonic and a coronary artery dilator, but there is recent evidence that this is not true. Cardiac efficiency has been shown to decrease with nikethamide, and coronary dilatation apparently occurs only with the use of toxic doses. 3. Nikethamide is frequently considered nontoxic, but, with the ever increasing dosage advocated, the convulsive dose determined for animals (50 mg. per kilogram of body weight) is being approached and exceeded in human beings. The administration of divided doses is not without danger, since the rate of detoxification is slower than with picrotoxin or metrazol® (0.5 convulsive dose detoxified in 100 minutes). This agrees with the observations of Eckenhoff and Hafkenschiel, who found that 60 to 80 mg. per kilogram caused convulsions in 1 of 4 normal dogs, but when the same or decreased dose was repeated in 40 to 90 minutes, 3 of the 4 dogs had convulsions and died in one to two hours. Chakravarti found that if the amount of nikethamide needed to awaken mice was compared with the amount that was lethal, the drug was approximately twice as toxic as picrotoxin or metrazol.® 4. Comroe and Dripps have been unable to demonstrate that nikethamide stimulates the carotid body, an action which might have given it some claim to preference over metrazol® or picrotoxin.

The clinical evidence, however, indicates that nikethamide is helpful in the treatment of mildly depressive

states, such as from avertin® and the short-acting barbiturates. Tatum states, ". . . if life is not jeopardized through depression either coramine, caffeine or strychnine may effect arousal." Clinical reports advocate the use of nikethamide for the treatment of morphine depression, and in a series of patients suffering from opium poisoning it was found to be of value in all but the most severe conditions.

Strychnine.—Strychnine has its principal effect on the spinal cord; since most of the central depressants act on the medulla and the higher centers, it follows that strychnine cannot successfully combat these depressions. When it has been tested as an analeptic experimentally it has been found to be inferior to picrotoxin or metrazol.® The only possible rational use strychnine could have in analeptic therapy would be as an adjunct to other analeptics to improve muscle tone, and this seems an insufficient reason for one's continuing its use.

Sympathomimetic Amines.—As mentioned at the beginning of this report, sympathomimetic drugs to be used as analeptics should be those in which the central stimulant action is relatively strong and the peripheral sympathomimetic effect relatively weak; this includes amphetamine (benzedrine®), d-amphetamine (dexedrine®) and desoxyephedrine (methedrine®).

Amphetamine has been used in the treatment of psychic depressant states, but the drug has not been tested sufficiently to warrant definitive statements as to its efficacy in narcotic depressant states. A series of 14 cases of barbiturate poisoning has been reported in which amphetamine was used to effect 13 recoveries, but a careful survey revealed that 9 of the patients would probably have recovered without such treatment. Handly and his co-workers favored the use of amphetamine in the treatment of morphine poisoning, but their series was very small. When the drug is used as an analeptic, there is some evidence that it is toxic and it also may cause slight analgesia. The use of amphetamine or other sympathomimetic amines alone as analeptics should be reserved until further data are forthcoming, but these drugs may profitably be combined with metrazol® or picrotoxin therapy.

Miscellaneous Drugs.—Studies of caffeine have shown it to be ineffective as an analeptic per se in moderate or deep narcosis. In normal subjects caffeine produces cortical stimulation, but when used in large doses in the treatment of narcosis it is inferior to other analeptics and is a depressant per se. It can be most effectively used as an adjunct to other analeptic agents. The use of camphor as a stimulant has almost ceased, and while alpha lobeline frequently exerts a decided, but brief, stimulant effect on respiration via the carotid body reflex, its effects are uncertain and usually followed by a period of depression due to a nicotinic action. Alpha lobeline is not to be recommended in view of the availability of other better analeptic drugs.

Succinate, Pyruvate and Fumarate.—The first attempt to use one of this group of substances in the treatment of depressant states was by Soskin and Taubenhaus, who found that sodium succinate shortened the duration of pentobarbital and amytal® anesthesia in rats and in 1 human being with barbiturate depression. Subsequent work on laboratory animals has failed to substantiate these observations in part or in whole. However, clinical reports have appeared claiming that succinate led to a decreased sleeping time in patients who had received thiopental sodium for anesthesia and facilitated the arousal of patients with barbiturate and morphine poisoning. In addition to succinate, pyruvate and fumarate have been investigated, but neither decreased the total depression time. There are apparently no reports of any of these substances having been used against severe depressant states.

At the present time the only justification for using these agents is that overdosage is not associated with convulsions. There is no other reason for one's substituting them for other standard analeptic agents at present. Further evaluation is needed, particularly as to what effect the diuresis produced by the agents has on their efficacy as analeptic drugs, before decision can be reached.

SOURCES OF ERROR IN CLINICAL REPORTS

Under the standard conditions of a laboratory investigation results obtained and conclusions drawn concerning the action of a given drug may differ considerably with the effect observed when the same drug is administered to patients. Animal weight, diet, hydration, season, mode of drug administration, rate of administration, interval between drug administration and onset of treatment and care of animals during treatment can all be standardized or controlled. The human patient presents an entirely different problem, which makes clinical investigation and the interpretation of its results more difficult. In the particular question at hand, species difference only partially explains the discrepancies of the laboratory and clinical reports, on the one hand, and the clinical reports from different institutions, on the other. The following discussion concerns factors that should be recorded during the treatment of any depressant state, since any of these factors may strongly influence the outcome of treatment. We would like to urge their inclusion in all clinical reports.

Renal Function.—Some of the depressant drugs are eliminated from the body primarily by excretion in the urine; this is particularly true of the longer-acting barbiturates. Failure to maintain an adequate urinary output may result in a retention of these barbiturates with a prolongation of narcosis. It is questionable whether an excessive output will increase the excretion of barbiturate over that which would be normally excreted, but in animals massive intravenous infusions started in less than 30 minutes after the barbiturates were administered shortened the sleeping time, presumably because of retention of a greater portion of the drug dissolved in body fluids, thus facilitating excretion. Urinary output and the type and amount of fluid intake should be recorded.

Visceral Pathologic Changes.—The existence of pathologic changes in body viscera, notably the kidney and liver, may lead to confusion in interpreting the results of analeptic therapy. Many of the depressants are detoxified in the liver; consequently a damaged liver will lead to a prolongation of a depression caused by any of this group of drugs. Renal damage will lead to a failure to excrete drugs normally eliminated through the urine. Summaries of case histories of depressant poisoning or analeptic therapy should always include notes of coexistent disease, even though at present there may seem to be no relationship between this and the depression.

Gastric Lavage.—Gastric lavage is an important early step in the treatment of depressant poisoning when the agent has been ingested. It, unfortunately, may

lead to confusion as to the amount of depressant actually absorbed. Careful notes should be made concerning the interval between drug ingestion and gastric lavage and of any evidence suggesting that some of the drug was removed with the lavage.

Time Interval Between Drug Administration and Onset of Treatment.—There are observations suggesting that the shorter the interval between drug administration and the onset of treatment, the more likely is the treatment to be successful. Certainly if the time interval is sufficient to allow irreversible tissue changes to occur, chances for recovery are materially shortened. The larger the dose of depressant the more important this interval would become. Wherever possible the clinician reporting on such cases should include this information.

Synergistic Action of More Than One Depressant.—When more than one agent has been responsible for the depression, the results of treatment may be obscured. Alcohol and the barbiturates act synergistically; and analeptics are then less effective. In laboratory animals, subconvulsive doses of morphine and analeptics led to convulsions, suggesting that the treatment of morphine or barbiturate plus morphine poisoning with analeptics may be ineffective. However, it must be remembered that morphine is not convulsant in human beings. Sulfonamide drugs and barbiturates may act synergistically, suggesting that antibiotics may be safer to use to prevent secondary infection in barbiturate poisoning.

Overstimulation with the Analeptic.—When overstimulation occurs during analeptic treatment, the evaluation of the case becomes difficult or impossible. The secondary depression following a convulsion, whether or not a barbiturate was needed to control the convulsion, may lead to a death when otherwise a successful outcome might be achieved.

When Analeptics Should Be Used.—If the mechanism of action of an analeptic can be accepted as a physiologic antagonism to a depressant drug, it follows that the analeptic should only be used when a drug depression exists. Anoxia and asphyxia are not indications for the administration of analeptics; adequate pulmonary ventilation with 100 per cent oxygen may lead to the reinstitution of respiration under these conditions when analeptics has failed.

CONCLUSION

In the light of the available published data the apparent mechanism of action of analeptics is a physiologic antagonism to depressant drugs, but in view of the needed investigation on the problem this can be no more than a tentative conclusion. Picrotoxin and metrazol® (pentamethylenetetrazol) are the most valuable analeptics obtainable today, with picrotoxin being the most potent, judging from laboratory research. Picrotoxin is also more dangerous to use and should only be used in deep depressions and then by someone well versed in its actions. Before the true part played by these drugs in the treatment of depressions can be fully evaluated, more complete and detailed clinical summaries must be made and compiled. The use of analeptics in the treatment of depressions should be only a part of a carefully integrated schedule of treatment including oxygen therapy, pressor drugs, fluid and pulmonary ventilation if necessary, as well as more than one analeptic if indicated.

Council on Physical Medicine

REPORTS OF THE COUNCIL

The Council on Physical Medicine has authorized publication of the following reports. HOWARD A. CARTER, *Secretary.*

BIRTCHER CRYSTAL BANDMASTER SHORT WAVE DIATHERMY, MODEL 800 ACCEPTABLE

Manufacturer: The Birtcher Corporation, 5087 Huntington Drive, Los Angeles 32.

The Birtcher Crystal Bandmaster Short Wave Diathermy Model 800 has the U. S. Federal Communications Commission's Type Approval Certificate no. D-482 and operates on a frequency of 13.56 megacycles. The necessity for crystal control has been explained in THE JOURNAL, Sept. 6, 1947, pages 30-31. The apparatus is listed by the Underwriters' Laboratories, Inc.

Birtcher Crystal Bandmaster S. W. Dia. Model 800

This unit is shipped complete in one box. In the box is found the unit itself, a treatment arm with corner casting and treatment drum, a magnetic inductance cable, a line cord and a book of operating instructions.

The weight of the unit is given as 61 Kg. (135 pounds); the shipping weight is 98 Kg. (215 pounds). The dimensions are 91 by 55 by 43 cm. (36 by 21½ by 16 inches). The unit requires a 110 volt alternating current supply, and draws 7.5 amperes, making the power consumption 750 watts.

The cabinet and chassis are all steel, mounted on 7.6 cm. (3 inch) ball bearing, ball swivel casters. Large 30.5 cm. (12 inch) handles are built onto the steel cabinet to make the instrument readily mobile about the hospital or clinic.

The specimen submitted by the manufacturer was given a thorough clinical trial, and the Council obtained convincing evidence of satisfactory results with both the inductance cable and the circular disk applicator.

The Council on Physical Medicine voted to include the Birtcher Crystal Bandmaster Short Wave Diathermy Model 800 in its list of accepted devices.

PRECISION TABLE HEARING AID ACCEPTABLE

Manufacturer: Precision Electronics Company, 850 West Oakdale Avenue, Chicago 14.

The Precision Table Hearing Aid is designed for use in schoolrooms, homes, offices and other institutions where 115 volt 50 to 60 cycle alternating current is available. It is a ruggedly built hearing aid that can be set on a table or desk. Such an instrument can be much more economical than the battery-operated wearable types. The hearing aid amplifies sound from 100 to 15,000 cycles per second and peaks at the speech frequency range.

The Model 3AC21 submitted for examination was found to be a 3 tube so-called desk or table instrument designed to work from 110 volt alternating current lines. The case is constructed of light colored plywood and presents the general appearance of a midget radio. It is equipped with a crystal microphone, mounted in the front of the case. Output impedances are provided for use in either high or low impedance phones. The Precision Table Hearing Aid Model 3AC21 is marketed with dynamic or moving coil ear phones, crystal phones, high impedance magnetic phones or with the miniature hearing aid type of phone.

Combination on-off switch and volume control and tone control knobs are mounted on the front of the case. The tone control attenuates the low frequency response of the instrument.

A "Hi-Lo" switch on the back of the instrument regulates the maximum power output of the amplifier. The "Hi" position is intended for use with persons who have extreme hearing impairments.

This instrument is designed for instruction of children too young to wear individual hearing aids.

Dimensions.—225 by 156 by 125 mm. (8⅞ by 6⅛ by 4 15/16 inches).

Weight.—2.52 Kg. (5 pounds, 9 ounces).

Power Consumption.—21 watts.

Acoustic Gain for Speech.—The maximum gain for speech is limited by acoustic feedback. Consequently, the values obtained on hard-of-hearing persons reflect in part the tightness of the seal of the phones against the ears, the position of the subject in relation to the instrument and his distance away from it. Two adults who wear individual hearing aids, each with predominantly middle ear impairments of approximately 50 decibels, in a test perceived speech at a sound pressure level 40 to 44 decibels lower with this instrument than without it before feedback or squealing occurred while sitting about 4 feet from the aid.

Both preferred the quality of the dynamic and the crystal phones to the magnetic phones and the miniature hearing aid type crystal receiver.

A phonograph input jack, which is provided in order that parents may take advantage of records for the speech training of hard of hearing children, is available for use with this instrument.

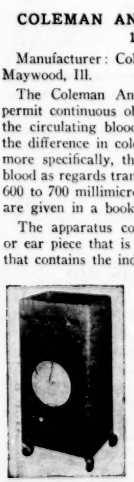
The Council on Physical Medicine voted to include the Precision Table Hearing Aid in its list of accepted devices.

COLEMAN ANOXIA PHOTOMETER, MODEL 17A, ACCEPTABLE

Manufacturer: Coleman Instrument Inc., 318 Madison Street, Maywood, Ill.

The Coleman Anoxia Photometer is a device designed to permit continuous observation of the degree of oxygenation of the circulating blood of the intact human subject. It utilizes the difference in color between oxidized and reduced blood, or, more specifically, the difference between oxidized and reduced blood as regards transparency to red light of wavelength between 600 to 700 millimicrons. Further details of theory and practice are given in a booklet of instructions.

The apparatus consists essentially of two parts, a receptor or ear piece that is attached to the subject's ear and a cabinet that contains the indicating or recording instruments. The two parts are connected by a cable. The ear piece bears a light which shines through the more translucent parts of the external ear and is analyzed by the use of filters and photoelectric devices. The cabinet measures 94 by 36 by 46 cm. (37 by 15 by 18 inches). The apparatus weighs 57 Kg. (125 pounds); the domestic shipping weight is 73 Kg. (160 pounds), and the foreign is 95 Kg. (210 pounds). It requires a 115 volt alternating current supply, and draws 1 ampere or 115 watts.



Coleman Anoxia Photometer, Model 17A.

The instrument is available in two forms, the indicating and the recording. The indicating form utilizes a projection galvanometer that permits the observer to read the patient's relative oxygen saturation at any time; it is called Model 17-000. The recording form includes a device, separately housed, that provides a continuous record; it is Model 17-400. There is a third modification, Model 17-410, that includes all parts (with the exception of the ear pieces) in a single case. All models are provided with storage batteries to assure the constant voltage needed for their operation; there is also a battery charger that can be brought into action simply by closing a charging switch.

In practice, the ear piece is attached to the patient and the instrument is set at some assumed saturation level; thereafter the instrument will respond over extended periods to variations in saturation. If absolute instead of relative values are desired, the instrument must be calibrated on the basis of direct chemical determinations of the oxygen content of the blood by customary laboratory methods.

The Council on Physical Medicine voted to include the Coleman Anoxia Photometer, Model 17A, in its list of accepted devices.

SONOTONE HEARING AID, MODEL 900 ACCEPTABLE

Manufacturer: Sonotone Corporation, Elmsford, New York.

The Sonotone Hearing Aid, Model 900, is a so-called one piece three tube air or bone conduction instrument, the batteries of which are contained in the amplifier case. The front half of the case is constructed of metal with a rhodium finish and the back of the case is made of gray plastic. The lower half of the back of the case is hinged to give access to the battery compartments. Two different air conduction magnetic receivers, R-1 and R-2, and two different bone conduction oscillators, 01 and 02, are available for use with this instrument. The R-2 receiver has the wider frequency range, especially for the higher frequencies. The R-1 receiver is more efficient (more sensitive) for frequencies below about 1,800 cycles. The 02 bone conduction emphasizes the amplification of the higher frequencies more than the 01 receiver.

Sonotone Hearing Aid, Model 900.

Two wheel type controls are situated at the top of the case. One is a volume control; the other is a combination on-off switch and three position tone control—3 dot position for maximum wide range frequency response, 2 dot position for low frequency attenuation and 1 dot position for low frequency attenuation and about 10 decibel decrease in over-all amplification efficiency. A detachable wearing or attachment clip can be fastened either to the front or the back of the case. An extra battery cord is obtainable, which permits a large size external A battery to be used with this instrument for more economical operation if desired.

A series of tests gave the following data:

Dimensions.—111 by 67 by 25 mm. (4⅜ by 2⅝ by 1 in.).

Weight.—200 Gm., including batteries (7¼ ounces).

Battery Drain:

		Measured Voltage	Measured Current
A, Zinc and Carbon,	1.5 volts	1.4 volts	45 milliamperes
B, Zinc and Carbon,	22.5 volts	21.0 volts	0.56 milliampere

Acoustical Gain, Pure Tones:

Receiver	Tone Control Position	250	500	1000	2000	3000	4000 cycles
R1	3 dot	46.0	47.0	56.5	57.5	60.0	33 db.
R1	2 dot	34.5	41.5	54.5	57.0	60.0	33 db.
R1	1 dot	22.5	29.5	54.0	50.0	53.5	28 db.
R2	3 dot	36.5	32.5	38.5	51.5	63.5	41 db.

The gain of the bone conduction receiver was obtained in terms of gain for speech as described immediately below.

Gain for Speech.—The gain for air conduction with the R1 receiver, 3 dot tone control position, was 50 decibels, with maximum gain setting of the volume control. This gain was obtained on 2 different hard of hearing persons having predominantly middle ear types of impairment, each of whom is an experienced user of hearing aids and has approximately 60 decibels unaided loss for speech with a speech audiometer. These persons perceived speech with 50 decibels less intensity from the loud speaker of a high quality sound amplification system (speech amplifier) in a sound-proof room with the hearing aid than without it.

V 1
194

Equivalent gain for speech measurements with the 01 bone conduction oscillator, 3 dot tone control position, maximum volume setting, showed a gain for speech by bone conduction of 44 decibels. These measurements were obtained on 2 persons with approximately normal bone conduction acuity and uniform losses of 50 decibels for air conduction. Noise ascribable to clothing friction was reported to be low.

The Council on Physical Medicine voted to include the Sonotone Hearing Aid Model 900, in its list of accepted devices.

RADIOEAR PERMO-MAGNETIC HEARING AID (UNIPHONE ONE-PIECE MODEL) ACCEPTABLE

Manufacturer: E. A. Myers & Sons, Radioear Building, 306-308 Beverly Road, Mt. Lebanon, Pittsburgh 16.

The Radioear Permo-Magnetic Hearing Aid, Uniphone Model, is a three tube one piece hearing aid, designed to work in either an air conduction or a bone conduction receiver. The case is constructed of smooth, black or ivory plastic material, the lower front half of which opens to give access to the battery compartment. A magnetic type microphone and magnetic receivers are used with the instrument. Sound pressure variations reach the magnetic microphone diaphragm through recessed louvers on the side of the case adjacent to the microphone. This instrument is equipped with a "Phonemaster" coil adjacent to the microphone so that voice signals from the telephone may be picked up inductively and then amplified through the instrument's amplifier and miniature receiver. A wheel type combination on-off switch and volume control is located at the top of the case. A "Noisemaster" switch is on one side of the case and serves to attenuate both high and low frequencies in noisy environments if desired. A "Powerizer" switch, built into the amplifier chassis, makes it possible to regulate the maximum gain of the instrument over a 15 decibel range. The frequency response of the amplifier can be regulated by closing a hole in the microphone case and by adjusting the three position "Lo" and "Hi" tone-controls on the amplifier chassis. The "Powerizer" and tone control adjustments are accessible only after separating the front and back of the case.

Radioear Permo-Magnetic Uniphone Hearing Aid.

Dimensions: 168 by 64 by 25 mm. (6⅝ by 2½ by 1 inch).

Weight (including batteries, cord and air conduction receiver): 270 Gm. (9½ ounces).

Battery Drain:

		Measured Voltage	Measured Current
A, zinc and carbon,	1.5 volts	1.3 volts	40 milliamperes
B, zinc and carbon,	22½ volts	21 volts	0.19 milliampere

Acoustical Gain for Pure Tones:

Frequency	250	500	1,000	2,000	3,000	4,000 cycles
Maximum gain, air conduction	45	50	54	59	63	38 db.

Acoustical Gain for Speech: Two adults who wear hearing aids, each with predominantly middle ear impairments of approximately 50 decibels, perceived speech at a 44 decibel lower level by air conduction and 38 decibel lower level by bone conduction as measured by a speech audiometer. The "Phonemaster" reproduced speech at a level several (approx. 15) decibels higher than the average output level from telephone receivers.

The Council on Physical Medicine voted to include the Radioear Permo-Magnetic Hearing Aid, Uniphone One-Piece Model, in its list of accepted devices.

ALOETHERM CRYSTAL CONTROLLED SHORT WAVE DIATHERMY UNIT MODEL F-7300 ACCEPTABLE

Manufacturer: A. S. Aloe Company, Olive at Nineteenth Street, St. Louis 3.

The Aloetherm Crystal Controlled Short Wave Diathermy Unit Model F-7300 is an apparatus designed to deliver electromagnetic radiation with a frequency of 13.56 megacycles (22.12 meters), for administration of therapeutic heat to the tissues. The necessity for crystal control arises from the ruling of the Federal Communications Commission that it will be illegal to use, after July 1, 1952, any diathermy unit whose frequencies are not within assigned bands, in order to eliminate interference with commercial radio, amateur radio and television. The firm states that in general crystal control is the most effective and most widely used means of controlling the frequency range of diathermy apparatus, and that this method is less laborious and expensive than screening the treatment room.

The apparatus is contained within a case that can be moved about on casters. It is 107 cm. (42 inches) high, 66 cm. (26 inches) wide and 46 cm. (18 inches) deep. Without arms or cables it weighs 57 Kg. (125 pounds). When the drum is attached for use with the arm horizontally extended to its lowest vertical adjustment in the bracket and with the face of the drum parallel to the floor, the distance from the floor to the drum is 38 cm. (15 inches). When the arm is in full vertical extension with the drum at right angles to the floor the distance from floor to drum is 175 cm. (69 inches).

The unit operates on a 60 cycle alternating current of 110 to 120 volts. The chassis, bearing the transformers, condensers, tubes and crystal stage, can be lifted easily from the cabinet for inspection or servicing. With the apparatus there is furnished an electromagnetic treatment drum and electromagnetic inductance cable with spacers, a flexible arm and a line cord.

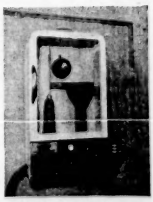
The firm submitted a report from a laboratory acceptable to the Council giving the results especially on phantom load tests made with Model F-7300. Measurements of the output in watts were made for both the inductance drum and the inductance cable, both the lamp load test and the isotonic calorimeter being used. The input ranged from 575 to 603 watts; the output, from 170 to 225 watts. Additional measurements were made in a laboratory acceptable to the Council on a specimen supplied by the firm, and the generally satisfactory workmanship, construction and performance of the apparatus were verified. It was noted that the apparatus is listed by the Underwriters' Laboratories.

The Council on Physical Medicine voted to include the Aloetherm Crystal Controlled Short Wave Diathermy Unit Model F-7300 in its list of accepted devices.

MEDIQUARTZ ULTRAVIOLET CABINET MODEL 420 ACCEPTABLE

Manufacturer: Medical Quartz Products Company, 5066 Santa Monica Boulevard, Los Angeles 27.

The Mediquartz Ultraviolet Cabinet Model 420 provides two sources of ultraviolet radiation. These are contained within a cabinet or box whose over-all dimensions are 41 by 23 by 12 cm. (16 by 9 by 4½ inches). It weighs 4.5 Kg. (10 pounds); the shipping weight is 6.8 Kg. (15 pounds). It operates on 110 volt alternating current and draws 69 watts. The cabinet is designed to be hung on a wall. Enameled with an ivory finish, it houses the controls in its lower portion; the upper portion has a glass door that gives access to the two ultraviolet generators. The cabinet contains the "Spot Irradiator" and the Orificial Applicator.



Mediquartz Ultraviolet Cabinet Model 420.

The Council on Physical Medicine voted to include the Mediquartz Ultraviolet Cabinet Model 420 in its list of accepted devices.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET - - CHICAGO 10, ILL.

Cable Address - - - - "Medic, Chicago"

Subscription price - - - - - Twelve dollars per annum in advance

Please send in promptly notice of change of address, giving both old and new; always state whether the change is temporary or permanent. Such notice should mention all journals received from this office. Important information regarding contributions will be found on second advertising page following reading matter.

SATURDAY, MARCH 19, 1949

THE VOICE OF THE AMERICAN MEDICAL ASSOCIATION

"The objects of the Association are to promote the science and art of medicine and the betterment of public health."—Constitution of the American Medical Association, Article 2.

"The legislative body of the Association is the House of Delegates."—Constitution of the American Medical Association, Article 6.

"The House of Delegates is composed of delegates elected by the constituent associations and by the sections of the Scientific Assembly and of delegates from the Medical Departments of the United States Army, the United States Navy, the United States Public Health Service and Veterans Administration, appointed by the Surgeon General or Chief Medical Director, as the case may be, of the respective service."—Constitution of the American Medical Association, Article 6.

These quotations from the Constitution of the American Medical Association define clearly where responsibility lies for determining the policies of the Association. No committee, council, board, officer or employee of the Association is charged with establishing policies for the American Medical Association. The Association has not now and never has had an official spokesman.

In the Organization Section in this issue of THE JOURNAL appears an announcement by Dr. Elmer L. Henderson, Chairman of the Board of Trustees, concerning the present activities of the Board of Trustees in relation to extending medical care. In February the Board of Trustees announced the twelve point program, which is an expansion of other programs which the House of Delegates accepted and announced over a number of years. In making this announcement the Chairman of the Board of Trustees is not establishing any new policies. The announcement is made for information of the medical profession and the public concerning the activities of the Board of Trustees.

The employees of the American Medical Association now number about 800. Many councils, committees and bureaus are charged with specific duties by the Constitution and By-Laws. The President of the Association is elected annually as President Elect and succeeds to office one year following his election. His duties are specifically defined by the By-Laws, as are also the duties of each of the councils, committees and officers. All officials of the Association, including the President, the President Elect, the Secretary and the Chairman of the Board of Trustees, make public appearances and are interviewed. When they speak, they endeavor to interpret the policies of the House of Delegates. The employees of the Association, including the General Manager, the Editor, the secretaries of the various councils and committees and the directors of the bureaus, also make many public appearances; when they speak or when they are interviewed, they also present the policies adopted by the House of Delegates.

Recently the Association has established a division of public relations and has employed special public relations counsel in connection with a program of education of the American people regarding the present status of medical care and the proposals that have been made for extension of medical care. These agencies represent the American Medical Association. When they issue releases to the press or make public pronouncements, as they frequently do in delivering addresses, they also present the point of view of the House of Delegates.

The statements here made are intended to correct unwarranted misrepresentations as to the Association. The House of Delegates at the St. Louis session reaffirmed the point of view of the American Medical Association in its determined opposition to compulsory sickness insurance. The House of Delegates also recommended the widest possible extension of voluntary hospitalization and sickness insurance but did not consent to the formation of a national insurance company under the sponsorship of the American Medical Association. These are the two most prominent issues now discussed in editorial opinion throughout the United States. Until the House of Delegates acts to change a decision every council, bureau, officer and employee is bound by the prevailing actions of the House of Delegates.

CHOLINESTERASE INHIBITORS IN TREATMENT OF MYASTHENIA GRAVIS

The effectiveness of neostigmine in the treatment of myasthenia gravis is presumably based, at least in part, on the inhibiting power of this drug on cholinesterase. By controlling the enzyme, the specific function of which is to split acetylcholine, the transmission of the nerve impulse through the synapse at the myoneural junction in sufficient amount to create an adequate response in the skeletal muscle is, according to Nachmansohn,[1] thus made more certain. Similar action by other anticholinesterases, like physostigmine and

1. Nachmansohn, D.: The Role of Acetylcholine in Conduction, Bull. Johns Hopkins Hosp. **83**: 463-496 (Dec.) 1948.

strychnine, also prevents the rapid removal of the acetylcholine released during the passage of the nerve impulse. Further research has led to an investigation of some of the newer compounds known to inhibit cholinesterase, di-isopropyl-fluorophosphate (DFP), hexaethyl tetraphosphate (HETP), and tetra-ethyl pyrophosphate (TEPP).

Di-isopropyl-fluorophosphate, when given intramuscularly, definitely lowers plasma and red blood cell cholinesterase activity for long periods. Comroe [2] and his associates have shown that di-isopropyl-fluorophosphate can also improve muscle strength in patients with myasthenia gravis. Closely parallel results were found by Gaddum and Wilson [3] and by Harvey, Lilienthal, Grob, Jones and Talbot.[4] The gain in muscular power, however, despite the fact that di-isopropyl-fluorophosphate may lower the plasma cholinesterase to zero, is not as great as that obtained with neostigmine, and the unpleasant central nervous and gastrointestinal symptoms evoked by di-isopropyl-fluorophosphate preclude its use in amounts sufficient to produce adequate therapeutic effects. The reason for the relative failure of di-isopropyl-fluorophosphate as a therapeutic agent has not been fully determined. Since it is a highly lipid-soluble compound, whereas neostigmine is water soluble, it may not act at the myoneural junction as readily and efficiently as does neostigmine. The better results obtained by neostigmine, moreover, may be due to the possibility that it has a direct action on skeletal muscle that is not shared by di-isopropyl-fluorophosphate.

A second anticholinesterase compound recently given clinical trial in myasthenia gravis is hexaethyl tetraphosphate (HETP). The effects are not dissimilar to those seen with di-isopropyl-fluorophosphate, according to Westerberg and Luros,[5] but the toxic symptoms, except those of central origin such as persistent nausea and insomnia, are more readily controlled by atropine. The drug exerts a prolonged effect similar to that noted after the use of di-isopropyl-fluorophosphate, and, when it is combined with neostigmine, the clinical results are moderately satisfactory. The limitation of hexaethyl tetraphosphate results largely from its instability in aqueous solution, a physical property not yet overcome. The results of the early studies are mildly encouraging, but the value of hexaethyl tetraphosphate as an acceptable therapeutic agent has yet to be established.

Somewhat more satisfactory are the clinical responses observed after the use of a third anticholinesterase preparation, tetra-ethyl pyrophosphate (TEPP). Although the side effects are similar to those seen after the use of di-isopropyl-fluorophosphate or hexaethyl tetraphosphate, the dose can be more easily regulated, being more stable, and it is effective when given by mouth. Burgen, Kelle and McAlpine [6] found the drug a completely effective substitute for neostigmine, and, although it is from a third to a half as potent, its action lasted about twice as long. Tetra-ethyl pyrophosphate is more cumulative than neostigmine, but less so than di-isopropyl-fluorophosphate. Because of its cumulative action, the response is more even than that of neostigmine. Harvey,[7] moreover, found that when tetra-ethyl pyrophosphate was given in amounts sufficient to increase the muscular strength above a basic level, but not to a maximum degree, there was a significant potentiation of the effect of all subsequent doses of neostigmine. Thus the combination of tetra-ethyl pyrophosphate and neostigmine, given orally, would appear to be of value in augmenting the present treatment of myasthenia gravis by neostigmine alone. Toxic symptoms, however, are frequent, some of them overcome by atropine. Until these are eliminated, di-isopropyl-fluorophosphate, hexaethyl tetraphosphate and tetra-ethyl pyrophosphate are still not superior to neostigmine in the treatment of myasthenia gravis.

2. Comroe, J. H., Jr.; Todd, J.; Gammon, G. D.; Leopold, I. H.; Koelle, G. B.; Bodansky, O., and Gilman, A.: Effect of Di-Isopropyl-fluorophosphate (DFP) upon Patients with Myasthenia Gravis, Am. J. M. Sc. **212**: 641-651 (Dec.) 1946.

3. Gaddum, J. H., and Wilson, A.: Treatment of Myasthenia Gravis with Di-Isopropyl Fluorophosphate, Nature **159**: 680-681 (May 17) 1947.

4. Harvey, A. M.; Lilienthal, J. L., Jr.; Grob, D.; Jones, B. F., and Talbot, S. A.: Effects on Neuromuscular Function in Normal Subjects and in Myasthenia Gravis, Bull. Johns Hopkins Hosp. **81**: 267-292 (Oct.) 1947.

5. Westerberg, M. R., and Luros, J. T.: Clinical Use of Hexaethyl Tetraphosphate in Myasthenia Gravis, Univ. Hosp. Bull., Ann Arbor **14**: 15-17 (Feb.) 1948.

6. Burgen, A. S. V.; Kelle, C. A., and McAlpine, D.: Tetra-Ethyl-pyrophosphate in Myasthenia Gravis, Lancet **1**: 519-521 (April 3) 1948.

7. Harvey, A. McG.: Some Physiological Experiments of Nature in the Field of Neuromuscular Function: Tetra-Ethyl Pyrophosphate in the Treatment of Myasthenia Gravis, Potassium Deficiency, Potassium Intoxication, Proc. Inst. Med. Chicago **17**: 182-188 (Nov. 15) 1948.

DISCONTINUATION OF TEMPORARY APPROVALS OF RESIDENCIES

Elsewhere in this issue is an announcement by the Council on Medical Education and Hospitals that the Council will no longer grant temporary approval to residency training programs. Henceforth residencies will be considered for approval only after they have been inspected by representatives of the Council. By this action the Council has returned to its traditional policy of approving only those institutions which have actually been inspected by its representatives.

At the end of the war the tremendous expansion of residency training programs to accommodate returning veterans made it essential that a procedure be developed which would permit the prompt handling of the large number of applications for approval of newly created residencies. Accordingly, in February 1946, the Council in conjunction with the Advisory Board for Medical Specialties and the individual American Boards adopted a plan of granting temporary approval pending inspection to hospitals that submitted sufficient information about their training programs to enable the Council to make a tentative evaluation of their adequacy. Hospitals granted temporary approval were inspected as quickly as possible, and after inspection either they

were given full approval or their approval was withdrawn. This program of granting temporary approvals made it possible in the space of three years to increase the number of approved residencies from just over 5,000 to more than 15,000. In general the program worked well, although instances occurred in which hospitals were granted approval when they would not have been granted approval had they actually been inspected.

The expansion of residency training has not halted, and it will now be possible to inspect all hospitals making application before granting approval. Approval based on the actual inspection of a hospital is essential for the maintenance of high standards of graduate training. Those hospitals holding temporary approval as of Jan. 1, 1949 will continue to hold such approval until they are inspected and decision is reached whether to grant them full approval or to withdraw approval.

The problem of appraising residency programs during the last three years has placed a burden on the Council and the American boards which cooperate with the Council. While delay in acting on applications has been unavoidable in many cases, the Council and the boards may take pride in the fact that during the period in question under their guidance the opportunities for residency training in the United States were more than trebled without any serious lowering of quality.

MORTALITY AND MORBIDITY STUDIES ON GROUP INSURANCE

A study of the frequencies of operations performed on employees and their dependents covered by group insurance contracts, and the charges made by the doctors for such operations, has just become available.[1] The claims studied were made in the periods from March 1946 to June 1947. The physicians' fees were collected from March 1947 to October 1947. Obstetrical benefits were omitted from this study.

The group of operations included tonsillectomy, appendectomy, benign tumor, hemorrhoidectomy, fracture, hysterectomy and herniotomy, which accounted for 58 per cent of the operations among employees and 69 per cent among the dependents. Tonsillectomy alone accounted for 60 per cent of the operations among children. The frequency for female employees was 23 per cent of all operations, and boys required 15 per cent more operations than girls.

When more than one operation was performed, the major operation or surgical procedure was coded as the first procedure; if it was not possible to make such a decision, the first procedure was determined by the largest reimbursement. The average reimbursement for multiple procedure claims was about twice that for single procedure claims. Female employees and wives of employees required more multiple operations than did the males; 24 per cent for female employees and 31 per cent for wives. Multiple procedure claims were reported in 17 per cent of the cases, with gynecology reaching a high of 51 per cent of this group and eye, ear, nose and throat operations at the other extreme of only 5 per cent. The most common combination of operations was hysterectomy and appendectomy, which represented 6.2 per cent of the total.

Most surgical treatment was performed in the hospital, but some was done out of the hospital; the reimbursement was lower for the latter type, usually less than 50 per cent of that for the inhospital surgical treatment. About 20 per cent of the employee operations and 13 per cent of the operations on dependents were performed out of the hospitals. Males had the largest amount of surgical treatment out of the hospitals.

The ratio of the reimbursement to the doctor's charge was about 54 per cent for all employees and 56 per cent for dependents. For the whole group it was 55 per cent. For every specific procedure the average charge for inhospital claims was greater than that for out of hospital claims; this reflects the tendency to perform the more serious operations in the hospital. In about 50 per cent of the cases the doctor's charge was not more than 92 per cent of the average charge per claim under the schedule of $150 maximum reimbursement; this is true for both inhospital and out of hospital claims. In 60 per cent of the cases the doctor's charge was not more than 106 per cent of the average charge.

1. Reprinted from the Tr. Actuarial Soc. America **49**: (May) 1948.

Current Comment

EXCERPTA MEDICA

When the periodical *Excerpta Medica* was established in Holland, the authorities approached the American Medical Association with a view to a cooperative effort in the indexing and abstracting of medical periodicals. As a result of negotiations between Dr. M. W. Woerdeman, professor of anatomy and embryology in the University of Amsterdam, who is chairman of the board of editors, Dr. Morris Fishbein, Editor of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, has been appointed one of the chief editors of *Excerpta Medica*. Studies are now in process to determine whether or not it will be feasible to indicate in the *Quarterly Cumulative Index Medicus* the articles that are abstracted in *Excerpta Medica* and also to utilize the services of the Dutch organization in the indexing of a greater number of periodicals than is now possible in the *Quarterly Cumulative Index Medicus*. UNESCO is also greatly interested in the development of a single international abstract of the important medical literature of the world. Conceivably from all these efforts great progress will be made in indexing and abstracting medical periodical literature.

ORGANIZATION SECTION

Official Notes

POLICY OF BOARD OF TRUSTEES FOR ACTION ON 12 POINT PROGRAM

In May 1948 a National Health Assembly was called by Federal Security Administrator Oscar Ewing in which all groups with an interest in medical care were represented. The assembly met in sixteen sections, each of which brought in a report constituting a plan for progress in health activities. The reports of these sections have not yet become available except for the inclusion of the condensed report of the section on medical care, by the Federal Security Administrator, in a report entitled "The Nation's Health: A Ten Year Program," published in September 1948.

When the full reports become available, the valuable material developed at the National Health Assembly may well serve as a basis of discussion and implementation of any program for the extension of medical care. When the National Health Assembly adjourned, most of those in attendance believed that the executive committee would carry on the studies and recommendations of that conference, but thus far only one meeting has been held. Otherwise, as far as can be determined, nothing has been done. The American Medical Association is ready to assume leadership in carrying out the recommendations of all of the sections which do not disagree with the fundamental policies established by the House of Delegates of the American Medical Association. Apparently the one point of issue remains the question of compulsory sickness insurance. The report of the section on medical care recommended the widest possible extension of voluntary hospitalization and sickness insurance. The House of Delegates at its meeting in St. Louis again reaffirmed its opposition to a system of compulsory sickness insurance.

The Board of Trustees of the American Medical Association is in constant touch and holds frequent conferences with various consumer groups and organizations. Proposals have been made for the American Medical Association to call another national health conference. It would be impractical to try to assemble another health conference until the report of the Assembly held in 1948 becomes generally available and until the reaction of the professions concerned and the public to those reports can be developed. The Board of Trustees wishes it clearly understood that it is prepared at the proper time not only to continue conferences already instituted but to call conferences with other consumer groups and to do whatever else is necessary to assure a better distribution of the high quality of medical care now existing in the United States.

ELMER L. HENDERSON, M.D.
Chairman, Board of Trustees,
American Medical Association.

MAYO CLINIC GROUP MEETS ASSESSMENT

Following is a letter sent by representatives of the Mayo Clinic and the Mayo Foundation to the secretary of the medical society with which they are affiliated:

Dr. H. M. Carryer, Secretary-Treasurer
Olmsted-Houston-Fillmore-Dodge County Medical Society
Mayo Clinic
Rochester, Minnesota

Dear Doctor Carryer:

In payment of the assessment of $25.00 requested of each of its members by the American Medical Association, we are pleased to transmit to the Olmsted-Houston-Fillmore-Dodge County Medical Society the attached check for $13,750.00. This sum is the payment of 210 members of the staff of the Mayo Clinic and 340 fellows of the Mayo Foundation, which is 97.7 per cent of the staff and 99.7 per cent of the fellowship personnel who are members of the local county medical society. The names of the individual physicians are attached. The figures given are exclusive of 20 staff members and 26 fellows who have not yet had the opportunity to contribute because of illness or absence from Rochester. There is every reason to believe that the response of this group will be equal to that cited above.

The members of the staff and the fellows of this institution are well aware of the efforts of the American Medical Association to devise methods for distributing medical care more widely by means of voluntary prepayment plans, and, almost unanimously, they desire to support these efforts.

It is to be hoped that such methods for extending medical care as might be devised by the American Medical Association will safe-guard or even improve the present high quality of medical service, and that the program will be such as to enlist the continued whole-hearted support of virtually all the physicians of the country. It is highly desirable that physicians present a united front in efforts to improve the distribution of medical care.

ARLIE R. BARNES, M.D., Chairman
Board of Governors, Mayo Clinic
VICTOR JOHNSON, M.D., Director
Mayo Foundation for Medical
Education and Research

Washington Letter

(From a Special Correspondent)

March 14, 1949.

Hoover Commission Recommends New Agency

Establishment of a new federal agency—the United Medical Administration—to administer virtually all of the government's medical and hospital care, medical research and public health activities has been recommended by the Hoover Commission. As described in the official report just submitted to Congress, the United Medical Administration would absorb the United States Public Health Service, practically all continental hospitals of the armed forces and all medical-hospital functions of the Veterans Administration.

Effectuation of the Hoover Commission's proposals depends on (1) willingness of Congress to give President Truman the reorganization authority which he has requested and (2) the President's choice in the matter. Dr. Paul B. Magnuson, chief medical director of Veterans Administration, is on record in favor of the principle of consolidating federal medical services. Medical departments of Army and Navy are strongly opposed to relinquishing any of their hospitals. The Federal Security Agency, of which U. S. Public Health Service is a component, supports inclusion of federal medical services in the proposed Department of Welfare, rather than establishment of an independent United Medical Administration, responsible directly to the President, as recommended by the Hoover Commission.

As Secretary of Defense, James Forrestal abstained from participating in preparation of the report. Of the other eleven members, opinion was sharply divided over the major issue considered, whether or not a new agency should be set up. Scarcely a majority reached agreement on the United Medical Administration plan. Chairman Herbert Hoover and former Representative Carter Manasco dissented from the majority provision that the agency be served by a board that would be advisory only. Army, Navy, Air Force and Veterans Administration would be represented on the board. Representative Clarence J. Brown wrote a separate opinion protesting vigorously against absorption of military hospitals by a civilian branch of the federal government. Another member of the Commission, Senator John L. McClellan, concurred. Another minority opinion was submitted by Secretary of State Dean Acheson (vice chairman of the Hoover Commission), Senator George D. Aiken and James Rowe Jr., advocating integration of health

services with education and security functions in a Department of Welfare.

The military would retain overseas hospitals, but all situated in this country would be surrendered, except certain station hospitals in outlying areas and one general hospital to be kept by each of the three armed services for research and teaching purposes. The plan further proposes that "professional personnel of the services might be assigned to the new administration for duty, research and training."

Indian hospitals and those administered by the Bureau of Prisons, Atomic Energy Commission, Tennessee Valley Authority and U. S. Soldiers Homes in Washington and Philadelphia would not be transferred. The proposed United Medical Administration, says the report, should be headed by "an outstanding administrator," but it is not required that he be a physician.

Ellender Defines His Position on Health Legislation

Senator Allen J. Ellender (Democrat, Louisiana) made it clear on March 5 that he is opposed to the Murray-Wagner-Dingell bill. The occasion was his weekly transcribed radio talk, broadcast by several Louisiana stations. He set forth his position on the health issue because several days earlier a news report had stated erroneously that he sided with Rep. John D. Dingell (Democrat, Michigan) in a televised debate in which the case against compulsory sickness insurance was argued by Senators H. Alexander Smith (Republican, New Jersey) and George W. Malone (Republican, Nevada). Actually, participants in the debate were Senator James Murray (Democrat, Montana) and Representative Dingell versus Senators Ellender and Malone.

"I want to again emphatically state," said Senator Ellender on March 5, "that I am opposed to socialized medicine in any form. I am opposed, specifically, to the President's compulsory health insurance plan now pending before Congress."

Representative Priest Heads Health Subcommittee

Representative J. Percy Priest (Democrat, Tennessee) has been appointed chairman of the newly formed subcommittee on public health, science and commerce of the House Committee on Interstate and Foreign Commerce. Formation of the subcommittee, which will handle national health, science foundation, local public health units and virtually all other medical and health legislation introduced in the House, was announced March 3—exactly two months after convening of the Eighty-First Congress. Other members are (Democrats) Representatives George G. Sadowski (Michigan), Thomas B. Stanley (Virginia), William T. Granahan (Pennsylvania), Andrew J. Biemiller (Wisconsin) and George H. Wilson (Oklahoma) and (Republicans) Representatives Joseph P. O'Hara (Minnesota), Wilson D. Gillette (Pennsylvania), Hugh D. Scott Jr. (Pennsylvania) and John B. Bennett (Michigan).

Under the chairmanship of Representative Priest, who also holds the important post of "whip" of the House Democratic membership, it will be up to the subcommittee to decide whether public hearings shall be held on the Murray-Wagner-Dingell bill, numerous special disease bills (multiple sclerosis, arthritis, epilepsy, cerebral palsy and others), proposed amendments of the Hill-Burton hospital survey and construction act, federal subsidization of local public health units and all enabling legislation involving the U. S. Public Health Service.

Hearings Open on Veterans Hospital Cutback

Scheduled to last for at least two weeks, hearings were opened March 10 by a special subcommittee of the Senate Labor and Public Welfare Committee on the proposed curtailment of the veterans hospital expansion program. Witnesses representing the American Legion and the Veterans of Foreign Wars, among the first to be heard, denounced President Truman's executive order of January 10 canceling plans for construction of twenty-four hospitals and reducing the size of fourteen others in order to effect a 16,000 bed cutback. Senator Claude Pepper (D., Fla.), chairman of the subcommittee, is opposed to the order, although he rarely takes exception to Truman policies. He has invited veterans' leaders, medical societies and public agencies in the nineteen affected states to send representatives here to testify on the cutback, with hearings scheduled to proceed until March 26.

Coming Medical Meetings

Alabama, Medical Association of the State of, Montgomery, April 19-21. Dr. Douglas L. Cannon, 519 Dexter Ave., Montgomery 4, Secretary.

American Association for Thoracic Surgery, New Orleans, March 29-31. Dr. Brian Blades, George Washington University Hospital, Washington, D. C., Secretary.

American Association of Anatomists, Philadelphia, April 13-15. Dr. Normand L. Hoerr, 2109 Adelbert Road, Cleveland 6, Secretary.

American Association of Genito-Urinary Surgeons, White Sulphur Springs, W. Va., Greenbrier Hotel, May 9-11. Dr. Norris J. Heckel, 122 S. Michigan Ave., Chicago 3, Secretary.

American Association of Industrial Physicians and Surgeons, Detroit, Book-Cadillac and Statler Hotels, April 5-9. Dr. Edward C. Holmblad, 28 E. Jackson Blvd., Chicago 4, Managing Director.

American Association of Pathologists and Bacteriologists, Boston, April 15-16. Dr. Howard T. Karsner, 2085 Adelbert Road, Cleveland, Secretary.

American Association on Mental Deficiency, New Orleans, Hotel Roosevelt, April 27-30. Dr. Neil A. Dayton, Box 51, Mansfield Depot, Conn., Secretary.

American Broncho-Esophagological Association, Chicago, Drake Hotel, April 18-19. Dr. Edwin N. Broyles, 1100 N. Charles St., Baltimore 1, Secretary.

American College of Allergists, Chicago, April 14-17. Dr. Fred W. Wittich, 423 LaSalle Medical Bldg., Minneapolis 2, Secretary.

American College of Physicians, New York, March 28-April 1. Dr. George Morris Piersol, 4200 Pine St., Philadelphia 4 Secretary General.

American Industrial Hygiene Association, Detroit, Book-Cadillac and Statler Hotels, April 5-7. Dr. Henry F. Smyth Jr., 4400 Fifth Ave., Pittsburgh 13, Executive Secretary.

American Laryngological, Rhinological and Otological Society, Chicago, Drake Hotel, April 18-20. Dr. C. Stewart Nash, 277 Alexander St., Rochester 7, New York, Secretary.

American Orthopsychiatric Association, Chicago, Stevens Hotel, April 4-6. Nina Ridenour, Ph.D., 25 W. 54th St., New York 19, Secretary.

American Pediatric Society, Atlantic City, May 5-6. Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12, Secretary.

American Physiological Society, Detroit, April 19-22. Dr. Milton O. Lee, 2101 Constitution Ave., Washington 25, D. C., Executive Secretary.

American Society for Clinical Investigation, Atlantic City, May 2. Dr. Paul B. Beeson, Grady Hospital, Atlanta 3, Georgia, Secretary.

American Society for Experimental Pathology, Detroit, April 18-22. Dr. Frieda S. Robscheit-Robbins, 260 Crittenden Blvd., Rochester, N. Y., Secretary.

American Society for Pharmacology and Experimental Therapeutics, Detroit, April 18-22. Dr. Harvey B. Haag, Medical College of Virginia, Richmond 19, Secretary.

American Society for Research in Psychomatic Problems, Atlantic City, Chalfonte-Haddon Hall, April 30-May 1. Dr. Sydney G. Margolis, 714 Madison Ave., New York 24, Executive Secretary.

American Society of Biological Chemists, Detroit, April 17-22. Dr. Otto A. Bessey, 1853 W. Polk St., Chicago 12, Secretary.

American Surgical Association, St. Louis, April 20-22. Dr. Nathan Womack, University of Iowa, Iowa City, Secretary.

Arizona State Medical Association, Tucson, May 8-10. Dr. Frank J. Milloy, 15 E. Monroe St., Phoenix, Secretary.

Arkansas Medical Society, Little Rock, April 14-16. Dr. William R. Brooksher, 602 Garrison Ave., Fort Smith, Secretary.

Association of American Physicians, Atlantic City, May 3-4. Dr. Henry M. Thomas Jr., 1201 N. Calvert St., Baltimore 2, Secretary.

California Medical Association, Los Angeles, May 8-11. Dr. L. Henry Garland, 450 Sutter St., San Francisco 8, Secretary.

Connecticut State Medical Society, New Britain, State Teachers' College, May 3-5. Dr. Creighton Barker, 258 Church St., New Haven, Secretary.

Federation of American Societies for Experimental Biology, Detroit, April 18-22. Dr. Milton O. Lee, 2101 Constitution Ave., Washington 25, D. C., Secretary.

Florida Medical Association, Belleair, April 10-13. Dr. Robert B. McIver, 111 West Adams St., Jacksonville, Secretary.

Georgia, Medical Association of, Savannah, Hotel De Soto, May 10-13. Dr. Edgar D. Shannon, 478 Peachtree St., N. E., Atlanta, Secretary.

Hawaii Territorial Medical Association, Honolulu, May 5-8. Dr. Harry L. Arnold Jr., 510 S. Beretania St., Honolulu, Secretary.

Iowa State Medical Society, Des Moines, April 18-21. Dr. Allan B. Phillips, 406 Sixth Ave., Des Moines 9, Secretary.

Kansas Medical Society, Topeka, May 9-12. Dr. D. D. Vermillion, 512 New England Bldg., Topeka, Secretary.

Louisiana State Medical Society, New Orleans, May 5-7. Dr. P. T. Talbot, 1430 Tulane Avenue, New Orleans 13, Secretary.

Maryland, Medical and Chirurgical Faculty of the State of, Baltimore, April 26-27. Dr. George H. Yeager, 1211 Cathedral St., Baltimore 1, Secretary.

Medical Library Association, Galveston, Texas, April 10-14. Miss Mildred R. Crowe, Medical College of Alabama Library, Birmingham 5, Ala., Secretary.

Michigan Postgraduate Clinical Institute, Detroit, Book-Cadillac Hotel, March 23-25. Dr. L. Fernald Foster, 2020 Olds Tower, Lansing 8, Mich., Secretary.

Minnesota State Medical Association, St. Paul, Municipal Auditorium, May 9-11. Dr. B. B. Souster, 496 Lowry Medical Arts Bldg., St. Paul 2, Secretary.

Mississippi State Medical Association, Biloxi, May 10-12. Dr. T. M. Dye, Box 295, Clarksdale, Secretary.

Missouri State Medical Association, Kansas City, March 27-30. Mr. T. R. O'Brien, 634 N. Grand Blvd., St. Louis 3, Secretary.

National Tuberculosis Association, Detroit, May 2-6. Dr. H. Stuart Willis, 1790 Broadway, New York 19, Secretary.

Nebraska State Medical Association, Omaha, Hotel Paxton, May 2-5. Dr. R. B. Adams, 416 Federal Securities Building, Lincoln 8, Nebraska, Secretary.

New Jersey, Medical Society of, Atlantic City, Hotel Ambassador, April 25-28. Dr. Earl L. Wood, 315 W. State St., Trenton 8, Secretary.

New Mexico Medical Society, Roswell, May 5-7. Dr. H. L. January, 221 W. Central Ave., Albuquerque, Secretary.

New York, Medical Society of the State of, Buffalo, Hotel Statler, May 2-6. Dr. Walter P. Anderton, 292 Madison Ave., New York 17, Secretary.

North Carolina, Medical Society of the State of, Pinehurst, The Carolina, May 9-11. Dr. Roscoe D. McMillan, P. O. Box 232, Red Springs, Secretary.

V 1
194

Ohio State Medical Association, Columbus, April 19-21. Mr. Charles S. Nelson, 19 E. State St., Columbus 15, Executive Secretary.
Rhode Island Medical Society, Providence, May 11-12. Dr. Morgan Cutts, 106 Francis St., Providence 3, Secretary.
Southern Branch, American Public Health Association, Dallas, Texas, Baker Hotel, April 14-16. Dr. George A. Denison, 600 S. Twentieth St., Birmingham, Ala., Secretary.
Southwest Allergy Forum, El Paso, Texas, Hotel Paso del Norte, April 4-5. Dr. O. E. Egbert, First National Bank Bldg., El Paso, Secretary.
Tennessee State Medical Association, Chattanooga, April 12-14. Dr. W. M. Hardy, 706 Church Street, Nashville 3, Secretary.
Texas, State Medical Association of, San Antonio, May 2-5. Dr. Harold Williams, 700 Guadalupe St., Austin, Secretary.
Western Association of Industrial Physicians and Surgeons, Los Angeles, Hotel Biltmore, May 7. Dr. Christopher Leggo, Crockett, Calif., Secretary.

Medical Legislation

STATE LEGISLATION

Connecticut

Bills Introduced.—H. 1063, to amend the workmen's compensation act, proposes to permit an injured employee a **free choice of physicians.** H. 1110 proposes that nothing in the general statutes shall be construed as prohibiting a physician licensed to practice medicine from prescribing any method or means for the **temporary prevention of pregnancy** in a married woman when in the opinion of such physician pregnancy would endanger the life or injure the health of such woman. H. 1413 and S. 901 propose the creation of a **system of health insurance.** H. 1577 proposes the appointment of a joint committee on public health and safety to "make an intensive investigation on the subject of **pain, sickness and death** and shall report to the governor not later than July 1, 1950, making recommendations for the elimination of pain, sickness and death." S. 657 proposes an appropriation to the state department of health to furnish services for children who have **cerebral palsy** or who are suffering from conditions which lead to cerebral palsy, such services to include the locating of the children, the provision of medical, surgical, corrective and allied services and care and the provision of facilities for hospitalization and after-care. S. 818 proposes to require physicians having knowledge that a wound has been caused as a result of the **discharge of a firearm** to report the same to the local prosecuting officer or state's attorney in the county in which he resides. S. 922 proposes to require all physicians and midwives to report all **cases of abortion** to the local prosecuting officer or the state's attorney in the county in which they reside. S. 965 proposes the establishment of an institution to be known as the Connecticut Center for **the Rehabilitation of Spastics** for the care, treatment, training and rehabilitation of spastics.

Idaho

Bill Introduced.—H. 290 proposes to authorize boards of county commissioners to levy a special tax to be used solely and exclusively for **preventive health services** by county boards of health.

Bill Enacted.—H. 34 has become chapter 23 of the Laws of 1949. It repeals and reenacts the existing medical practice act of the state with extensive amendments. Among other changes are the creation of an independent **state board of medical examiners**, provisions for the granting of temporary licenses and authorization to make use of the injunctive process in enforcing the provisions of the act.

Illinois

Bill Introduced.—S. 127 proposes the enactment of **a disability compensation act.**

Indiana

Bills Introduced.—S. 157, to amend the medical practice act, proposes to eliminate therefrom the provisions authorizing the use of **the injunctive process** to punish violators of the act. S. 259 proposes to make relevant in **actions involving illegitimacy** the results of blood tests of the complainant, her child and the defendant made to determine whether or not the defendant can be excluded as being the father of the child. The result of the test would be admissible in evidence only in cases where definite exclusion is established.

Iowa

Bill Introduced.—S. 339 proposes the enactment of a food and drug act providing, among other things, that any drug sold at retail and containing any quantity of **aminopyrine, barbituric acid, pituitary, thyroid** or their derivatives must be labeled in accordance with the provisions of the act unless it is sold on the written prescription of a doctor, dentist or veterinarian.

Kansas

Bills Introduced.—H. 200 proposes the enactment of a **board of nurse registration** and nursing education for the licensing of professional and practical nurses. Practical nursing would be defined by the proposal as meaning the performance for compensation, personal profit or gratuitously by members of religious communities, of such duties as are required in the physical care of a convalescent, a chronically ill or an aged or infirm patient, and in carrying out such medical orders as prescribed by a licensed physician, requiring a knowledge of simple nursing procedures but not requiring the professional knowledge and skills required for professional nursing. H. 307 proposes that regularly licensed schools for the purpose of **teaching chiropractic** shall have extended to them the same privileges as to the use of bodies for dissecting, demonstrating or teaching as those granted in this state to medical colleges.

Maine

Bill Introduced.—H. 1581, to amend the workmen's compensation act, proposes to permit injured employees to receive **chiropractic services.**

Maryland

Bills Introduced.—H. J. R. 11 **proposes that the Congress of the United States be memorialized not to enact legislation that has been proposed the effect of which will be to bring the practice of medicine in this country under federal direction and control.** H. 152, to amend the law relating to the **practice of chiropractic,** proposes, among other things, that a license to practice chiropractic shall not include the right to practice obstetrics. S. 244 proposes to amend the medical practice act so that the term "physician" shall be construed to **include chiropractic** as well as medical physicians.

Minnesota

Bills Introduced.—H. 419 proposes the enactment of a **disability benefits law.** H. 838, to amend the state narcotic act, proposes to include amidone, isoamidone, and keto-bemidome within the definition of **"narcotic drugs."** H. 1091 proposes to make it unlawful for any female to submit to the act or operation of **artificial insemination,** or for any person to perform the act or operation of artificial insemination upon any female, or to assist, aid or abet any person in the performance of such act, or to donate, distribute or collect semen therefor, unless such woman is married and her husband has consented in writing under oath to such act or operation, and only the semen of the husband is used therefor. A child born in accordance with the provisions of this act would be considered the legitimate, natural child of both the husband and the wife for all purposes.

Nebraska

Bill Enacted.—L. B. 48 was approved Feb. 15, 1949. It authorizes counties to create the office of coroner's physician and provides that such physician shall make **postmortem examinations** of bodies and give testimony as to the same without witness fees in all inquisitions and state and county cases when called by the coroner, county or state.

Nevada

Bill Introduced.—A. 122, to amend the law relating to vital statistics, proposes to require physicians to report to the proper law enforcement officer any death which occurs during the **administration of any anesthetic** or during a surgical operation or any other medical procedure.

New Mexico

Bills Introduced.—H. 243 proposes to repeal a law enacted in the 1947 session which required all practitioners of the healing art to **designate the school of practice** which they intend to practice on all stationery, signs, advertisements, etc. S. 195 proposes to amend the **osteopathic practice act** by repealing the "as taught" definition of osteopathy and substituting therefor the following: "Persons who treat human ailments by that system of the healing arts which places the chief emphasis on the structural integrity of the body mechanism as being the most important factor for maintaining the organism in health."

North Carolina

Bill Introduced.—S. 96 proposes that a **physician or midwife** having charge of a birth of a prematurely born infant shall immediately give notification thereof to the local health department of the county in which the infant was born. S. 150 proposes to require every physician to notify the local health officer of the name of any person by whom such physician is consulted professionally and who is found to have **cancer of any type.**

Ohio

Bills Introduced.—H. 99 proposes the creation of a classification to be known as **public health sanitarian** which would be defined to mean a person trained in the field of sanitary science and sanitary technology who is qualified to carry out educational and inspectional duties and to enforce the law in the field of sanitation. H. 444 proposes to make it a **misdemeanor** for any person not licensed to practice a profession in the state **to advertise** in any manner whatever leading the public to believe that he is authorized to practice such profession or to list his name in any directory, newspaper, magazine, etc., suggesting that he is authorized to practice such profession or to use in connection with his name any word, title, symbol, letters or abbreviations suggesting that he is authorized to practice such profession or to offer any service, advice, counsel or assistance such as is customarily offered or rendered by persons licensed to practice such profession. S. 133 proposes the creation of the state **naturopathic board of examiners** and defines naturopathy as that philosophy and system of the healing art embracing prevention, diagnosis and the care of and treatment of human ills, diseases, traumas, deformities and functions by the use of the several properties of air, light, heat, cold, water, mechanics, electricity, manipulation and psychology, together with the use of such substances, largely nutritional, of plant, animal or mineral origin as are naturally found in and required by the body. Naturopaths, by virtue of this proposal, would not be permitted to practice major surgery or use x-ray, radium and radioactive substances for therapeutic purposes or to prescribe for internal use any substance required by law to be labeled poison. S. 151 proposes to amend the **privileged communications** statute so as to include communications between a physician and his patient in certain instances.

Wisconsin

Bill Introduced.—A. 314, to amend the workmen's compensation act, proposes to make the employer liable for reasonable expense incurred by an employee for fees of physicians and other experts appearing as witnesses in his behalf.

GOVERNMENT SERVICES

ARMY

REORGANIZATION OF ARMY HOSPITALS TO CONSERVE MEDICAL PERSONNEL

The Surgeon General of the Army announced March 1 the proposed streamlining of wartime military hospitals in overseas theaters to effect greater economy in the use of personnel in scarce professional categories. The proposed organization is the result of a study of the experiences of the Army Medical Department in overseas theaters during combat. The main wartime obstacle was the lack of flexibility in the use of professional personnel inherent in the older and more rigid Table of Organizations, under which equipment and personnel were welded together as a unit. This concept required larger numbers of professional personnel and was responsible for much enforced idleness during the war. The proposed plan reduces the number and type of medical organizations and authorizes a split between equipment and administrative, on the one hand, and professional personnel on the other.

Under the new plan, which has the approval in principle of the General Staff, the "professional complement," as it will be called, will not join the unit until the last practical moment. In this way, the personnel in scarce categories will be available for use at other installations, or may even remain longer in the civilian community, until the time when they are actually needed with their parent unit.

"The idleness of valuable personnel had serious effects," the Surgeon General stated. "These professional men and women were not being used economically. More physicians, dentists, nurses and others were called into the service than necessary, creating a shortage in the civilian economy and adversely affecting morale in civilian as well as military medical circles."

The final details will be field tested in the near future. It is expected there will be more units consisting of equipment and administrative personnel than there will be professional complements. It is planned that the professional complements, once their duties in a hospital have been completed and the patients evacuated, will move as a team to another hospital unit which has been made ready in a more forward area of the combat zone. Professional complements will be further augmented by specialist teams as required. This will likewise contribute to greater utilization of specialists.

OFFICERS TO PURSUE ADVANCED CIVILIAN COURSES

The following medical officers have been accepted for advanced courses in the civilian schools and hospitals indicated:

Col. Wendell A. Weller, University of California, San Francisco, ear, nose and throat pathology.

Lieut. Col. T. Donald McCarthy, University of Kansas Medical Center, Kansas City, radiology physics.

Major Herbert P. Sube, University of California, San Francisco, ear, nose and throat pathology.

Capt. Ralph N. Kraus, University of California, San Francisco, ear, nose and throat pathology.

Capt. Marion E. McDowell, University of Rochester, School of Medicine and Strong Memorial Hospital, Rochester, N. Y., residency training in internal medicine.

Capt. Frederick F. Krauskopf, Jackson Memorial Hospital, Miami, Fla., assistant residency in surgery.

Capt. Richard A. Hayden, St. Mary's Hospital, Brooklyn, residency in obstetrics and gynecology.

Capt. Russel R. Jauernig, Bellevue Hospital, New York, residency in radiology.

Capt. Walter G. Olin Jr., Patterson General Hospital, Patterson, N. J., residency in pathology.

First Lieut. Bryan Williams Jr., Massachusetts Memorial Hospital, Boston, intern training.

First Lieut. Frederick Charles Biehusen, Grace-New Haven Community Hospital, New Haven, Conn., residency in pediatrics.

First Lieut. Arthur W. Adams, Ellis Hospital, Schenectady, N. Y., internship in surgery.

First Lieut. Norman Goldstein, Lincoln Hospital, New York, residency in pediatrics.

First Lieut. Robert Franklin Hufner, Meadowbrook Hospital, Hempstead, New York, residency in pathology.

First Lieut. Lester D. Johnson Jr., Georgetown University Hospital, Washington, D. C., residency in obstetrics and gynecology.

First Lieut. Ralph G. Thomas, Indianapolis General Hospital, Indianapolis, residency in general surgery.

First Lieut. John S. Kelly, Cook County Hospital, Chicago, residency in general surgery.

First Lieut. John A. Norman, Children's Hospital, Denver, residency in pediatrics.

First Lieut. John N. Palmer, Provident Hospital, Chicago, residency in surgery.

First Lieut. Harry Banoff, Los Angeles County General Hospital, residency in ophthalmology.

First Lieut. Charles B. Crow Jr., Boston City Hospital, Boston, assistant resident in medicine.

First Lieut. George R. Barnes Jr., Grace-New Haven Community Hospital, New Haven, Conn., residency in pediatrics.

First Lieut. Ben D. Hall, John Gaston Hospital, Memphis, Tenn., residency in medicine.

First Lieut. Saul B. Appel, New York University–Bellevue Medical Center, New York, residency training in medicine.

First Lieut. Willis H. Thornburg, New York Post-Graduate Medical School and Hospital, New York, residency in surgery.

First Lieut. Robert A. Simenson, Worcester State Hospital, Worcester, Mass., residency in psychiatry.

VACANCIES IN MEDICAL SERVICE CORPS

A number of vacancies in the grades of second and first lieutenant still exist in the Army Medical Service Corps in bacteriology, biochemistry, parasitology, serology, entomology, nutrition, toxicology, industrial hygiene, industrial hygiene engineering, optometry, psychiatric social work, clinical psychology and sanitary engineering, under the provisions of Department of Army Circular 210 dated July 14, 1948. Although most of the provisions of Circular 210 were suspended as of Feb. 15, 1949, pending completion by the Department of the Army of a study of remaining requirements, applications for reserve commissions in most grades are still being accepted by the Medical, Dental, Veterinary, Nurse and Women's Medical Specialist Corps as well as by the Medical Service Corps for appointment in the grades of second and first lieutenant.

THE DARNALL EXHIBIT

The Army Medical Library, Washington, D. C., has been conducting a series of exhibits entitled "Famous Men of Army Medicine." The subject of the seventh exhibit in this series is the late Carl Rogers Darnall, whose investigations and inventions made modern water purification possible. The method which, then Major, Darnall of the U. S. Army Medical Department originated in 1910 was the introduction into water supplies of chlorine gas, a method which has since been adopted throughout the world. Safe drinking water today is so universally obtainable that few persons recognize the great significance of modern water purification in relation to public health. The pictorial part of the exhibit concerns the application of the Darnall method both in the Pacific and European Theaters of Operation in World War II. Much of the Darnall experimentation to develop this method was carried on during his period of service on the faculty of the Army Medical School in Washington, D. C. Major Darnall later attained the rank of brigadier general and was awarded the Distinguished Service Medal for outstanding service in administering the activities pertaining to medical supply during World War I.

MONTHLY MEDICAL MEETING

At the Surgeon General's regular monthly meeting of medical officers at Walter Reed Hospital, February 17, Dr. Frank Meleney of the Department of Surgery, Columbia University, New York, spoke on "Bacitracin: Indications and Limitations of Its Systemic Administration in the Treatment of Infections." After the meeting refreshments were served in the Officers' Club.

PERSONNEL

Lieut. William J. Brown Jr., M.C., formerly at Ft. Lawton, Washington, D. C., has been assigned to the staff of the Army Institute of Pathology, Washington, D. C., as tissue pathologist.

NAVY

EXAMINATIONS FOR APPOINTMENT IN MEDICAL CORPS

Examinations for the selection of candidates for appointment to the grade of lieutenant (junior grade) in the Medical Corps of the Navy will be conducted at all Naval hospitals in the continental United States during the period April 4-8, 1949.

Graduates of approved medical schools in the United States or Canada who have completed intern training in accredited hospitals or who will complete such training within four months of the date of the examination, and who are physically and otherwise qualified, may be examined for appointment. Candidates must be less than 32 years of age at the time of appointment and will be required to appear before boards of medical examiners and supervisory Naval examining boards at the Naval hospital nearest their residence to demonstrate their physical and professional qualifications. After approval by the President of the United States and confirmation by the Senate, selected candidates will be issued appointment and orders assigning them to duty in a Naval medical facility.

As a result of the authorized additional compensation of $100 a month for medical officers, a lieutenant (junior grade) in the Navy Medical Corps receives pay and allowances totaling $5,011.00 a year if married and $4,575.00 if without dependents.

Information concerning procedure of application may be obtained from the nearest Naval Officer Procurement Office or from the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C. (Attn: Code-3424).

FIRST ACTIVE DUTY

The following lieutenants (jg) in the Medical Corps Reserve have been nominated for courses of instruction under the Navy's Graduate Medical Training Program: Wayne C. Brady of Statesville, N. C., to a residency in orthopedic surgery at Columbia Hospital of Richmond County, Columbia, S. C.; Ward Cooper Jr. of Palo Alto, Calif., to instruction in ophthalmology at the Naval Hospital, Oakland, Calif.; Raymond J. Leffler of Iowa City to a residency in pathology at Robert Packer Hospital, Sayre, Pa.; Wolfram G. Locher of Chardon, Ohio, to a residency in anesthesiology at Reading Hospital, Reading, Pa., and Robert G. Trout of Columbus, Ohio, to a basic course in surgery at the University of Pennsylvania Graduate School of Medicine, Philadelphia.

POSTGRADUATE INSTRUCTION

The following Regular Navy medical officers have been nominated for postgraduate courses of instruction as indicated:

Name	Residence	Course
Dement, Donald E., Capt.	Grosse Ile., Mich.	Training in the National Laboratories, Oak Ridge, Tenn.
Hoot, Paul M., Capt.	Ponca City, Okla.	Training in the National Laboratories, Oak Ridge, Tenn.
Kwiatkowski, Peter S., Lieut. Comdr.	Binghampton, N.Y.	Training in the National Laboratories, Oak Ridge, Tenn.
Yocum, Thomas D., Lieut.	Versailles, Ky.	Children's orthopedics at the Miller Orthopedic Clinic, Charlotte, N. C.
Fahrner, Robert J., Lieut. (jg)	Joliet, Ill.	Residency in obstetrics and gynecology at the Naval Hospital, Long Beach, Calif.
Gardipee, Charles R., Jr., Lieut. (jg)	San Francisco	Residency in general practice at the Naval Hospital, Long Beach, Calif.
Lewis, Garner L., Lieut. (jg)	Kingston, N. Y.	Training in the National Laboratories, Oak Ridge, Tenn.
Park, William F., Lieut. (jg)	Baltimore	Residency in otolaryngology at the Naval Hospital, Bethesda, Md.

PERSONAL

Lieut. (jg) Robert A. Loeffler of Medford, Ore., has been transferred from an active reserve status to the Medical Corps of the Regular Navy and is on duty at the Naval Hospital, San Diego, Calif., for a course in general surgery.

PUBLIC HEALTH SERVICE

STUDY OF PUBLIC HEALTH SERVICE GRANTS AND FELLOWSHIP PROGRAMS

On the recommendation of the National Advisory Health Council, a special committee has been appointed by the Surgeon General of the Public Health Service to study the Public Health Service research and educational grants and fellowships, the cost of medical education and the effect of these grants on medical school finances and on medical education. The purpose of this study is to evaluate existing grant and fellowship programs and policies and to provide a basis for advice on the financial needs of medical education. The members of this committee are:

Dr. Lowell J. Reed, Chairman
Dr. George Baehr
Dr. Robin C. Buerki
Dr. Edward A. Doisy
Dr. E. G. Gustavson
Dr. Algo Henderson
Dr. E. E. Irons
Dr. Carlyle Jacobsen
Dr. Hugh Morgan
Dr. B. O. Raulston
Dr. James S. Simmons
Dr. Herman B. Wells

The special committee has consulted with the Committee on the Survey of Medical Education, sponsored by the Council on Medical Education and Hospitals of the American Medical Association and the Association of American Medical Colleges. While the two committees will carry out their studies independently, every effort is being made to coordinate their activities with the view of avoiding unnecessary duplication of work and reducing the demands on the officers and faculties of the medical schools.

The study by the Surgeon General's committee will be conducted through a series of regional meetings of the deans and finance officers of the medical schools and through subsequent interviews by a representative of the committee. The first regional meeting will be held in Atlanta on March 21. Meetings in other regions are being scheduled for April.

NURSES NEEDED FOR GOVERNMENT POSITIONS

The U. S. Civil Service Commission announces an examination for Public Health Nurse for vacancies in Washington, D. C., and vicinities and others in territories and possessions of the United States. No written test is required. Applicants must have completed a three year nursing course or a two year nursing course plus appropriate experience or education, and they must have had a minimum of one year's experience in public health nursing in a generalized community public health program. All applicants must be registered as professional nurses in some state or territory at the time of appointment. These positions pay from $3,727 to $4,479 a year. Details and application forms may be obtained from the U. S. Civil Service Commission, Washington 25, D. C., or from most first and second class post offices. Applications must be on file with the Commission not later than March 29, 1949.

EUROPEAN INFLUENZA CENTERS

The Influenza Information Center, National Institutes of Health, has received a list of European influenza centers from Dr. C. H. Andrewes, World Influenza Centre, London. The centers were established as part of the World Health Organization Study Program. Following is the list:

Laboratoire Central d'Hygiene, Brussels, Belgium.
State Serum Institute, 80 Amager Boulevard, Copenhagen, Denmark.
Virus Laboratory, St. Vincent's Green, Dublin, Ireland.
Institut Pasteur, Rue du Dr. Emile-Roux, Paris XV, France.
State Laboratory, Ministry of Hygiene, Athens, Greece.
Institute of Hygiene, Budapest, Hungary.
University Institute for Experimental Pathology, Keldur, Iceland.
Instituto Sieroterapico Italiano, Naples, Italy.
University Laboratory, Oslo, Norway.
Swedish State Bacteriological Laboratory, Box 764, Stockholm 1, Sweden.
Institut de l'Hygiene publique "Refik Saydam," Ankara, Turkey.
Federal Institute of Epidemiology, Belgrade, Jugoslavia.

Medical News

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

CALIFORNIA

Multimillion Dollar Medical Building Program.—The regents of the University of California have approved the multimillion dollar building program to erect on the Los Angeles campus a complete medical research center. Scheduled for immediate construction is the $15,500,000 medical school and teaching hospital which will form the nucleus of the project on 35 acres at the south end of the Los Angeles campus and 34 acres nearby, recently deeded to the university by the United States government. The central structure will combine a medical school and a 500 bed teaching hospital, as well as provision for 114 additional student health service beds. The radiology department and surgical operating rooms will be built underground, representing an innovation in the construction of a modern hospital. Also unprecedented is the interior planning whereby classrooms and laboratories devoted to a particular medical subject will occupy the opposite wing on the same story as the corresponding ward in the training hospital, thus permitting students to examine appropriate patients without leaving the floor. Architecturally, the hospital-school will be flexible, with a modular system in 5 foot units providing infinite variety of floor plan arrangements and a peripheral piping system that makes possible the immediate conversion of any room into a fully equipped laboratory with the addition merely of fixtures. The exterior of the building has been designed to allow expansion in nine horizontal directions, and vertically to the Los Angeles height limit. Other buildings to be erected include a student health service, outpatients' clinic, interns' and nurses' quarters and library. Plans call for the addition of an atomic energy medical research unit, buildings devoted to mental hygiene and aviation medicine, cancer and cardiovascular research units. According to Dr. Stafford Warren, dean of the University's Los Angeles Medical School, the new center will represent "a full scale effort to coordinate the basic sciences and clinical sciences within the walls of a single university." Various academic departments of the university will be closely allied to related departments in the new center, with undergraduates in other departments sharing libraries, laboratories and even some classrooms with medical students.

COLORADO

Reporting of Animal Diseases.—The state department of public health has instituted a program of reporting animal diseases which are transmissible to human beings. Each veterinarian furnishes reports on forms designed for this purpose. Additional information may be obtained from Martin D. Baum, D.V.M., director, Veterinary Public Health Services, State Office Building, Denver 2.

Course in Problems of Newborn Infants.—A graduate course on The Problems of Newborn Infants, to be sponsored by the University of Colorado School of Medicine, Denver, and the Colorado State Division of Public Health, will be given at the University of Colorado Medical Center, Denver, April 7-9. Lectures, panel discussions and demonstrations will be given on obstetric aspects of prematurity, resuscitation, nutrition, isoimmunization, psychologic problems in prematurely born infants, community planning, infections and interpretation of laboratory findings in the newborn. The guest lecturer is Dr. Herbert C. Miller Jr., professor of pediatrics, University of Kansas School of Medicine, Lawrence-Kansas City. The course is open to graduates of medical schools approved by the American Medical Association. The registration fee is $5 and the tuition is $10. Interns and residents are invited to attend without charge. Inquiries should be directed to John Lichty, M.D., director of the course.

CONNECTICUT

State Cancer Conference.—The second annual State Cancer Conference of the Connecticut State Medical Society and the Connecticut Cancer Society will be held March 23 at the Hartford Club, Hartford. Visiting physician speakers include:

Oliver Cope, Boston, Radioactive Isotopes in Diagnosis and Treatment of Cancer.
Richard H. Sweet, Boston, Cancer of the Esophagus and Stomach.
William Dameshek, Boston, Leukemias.

Hospital for Alcoholism.—A publicly supported hospital devoted solely to the study, treatment and rehabilitation of alcoholic addicts of the state is to be erected in Hartford within the next year. Funds totaling $551,943 have been made available by the state for the two story structure which will have accommodations for 50 bed patients and an outpatient department to treat about 400 ambulatory patients annually. It will be directed and operated by the Connecticut Commission on Alcoholism. Treatment will be entirely professional in character with full medical, psychiatric, nursing and social work service available. It will serve as a pilot and demonstration center through which various therapeutic technics can be evaluated. It will undertake the study and treatment of the voluntary type of alcoholic addict who seeks assistance and the patient with a long history of court appearances for chronic alcoholism.

DISTRICT OF COLUMBIA

Dr. James G. Cumming Retires.—Dr. James Gordon Cumming will retire as director, Bureau of Preventable Diseases, of the District of Columbia Health Department after twenty-four years of service. After graduation from the University of Michigan in 1903, Dr. Cumming taught at the medical school until 1914 and was director of the university's Pasteur Institute. From 1914 to 1918 he served as director of the Bureau of Communicable Diseases, California State Department of Health, and was lecturer in preventive medicine at the University of California Medical School, Berkeley–San Francisco. For World War I service in connection with studies of epidemic influenza and pneumonia Dr. Cumming was awarded the Distinguished Service Medal. He was assigned to the Office of the Surgeon General of the Army in Washington to assist in the preparation of the medical and surgical history of World War I. Dr. Cumming plans to retire to his farm in Indian Head, Md.

GEORGIA

School of Medical Illustration.—The first school of medical illustration in Southeastern United States has opened at the University of Georgia School of Medicine, Augusta. Work is available for medical students and for medical art students who wish to take advanced work in a particular branch and to scientific illustrators. A regular four year course for beginners is also available. A limited number of applicants are selected each year. Applications for admission may be addressed to the Registrar, University of Georgia School of Medicine, Augusta.

ILLINOIS

Appointments to Crippled Children's Committee.—Nine new members, each to serve two years, have been appointed to the Professional Advisory Committee of the Division of Services for Crippled Children by the University of Illinois Board of Trustees. Five appointees from Chicago are: Mr. Ray E. Brown, superintendent of the University of Chicago Clinics; Drs. Francis J. Gerty and H. Worley Kendell, University of Illinois College of Medicine; Dr. Meyer A. Perlstein, and Miss Jane Bull, executive director of the Illinois Commission for Handicapped Children. Others are Mr. Isaac Jolles, State Department of Public Instruction, Springfield; Drs. Stuart Broadwell Jr., Springfield otologist; Frederick H. Maurer, Peoria pediatrician, and Harold Westlake, Ph.D., Northwestern University.

Chicago

Davis Lecture on Medical History.—Paul M. Angle, LL.D., director of the Chicago Historical Society, will give the sixth annual D. J. Davis Lecture on Medical History March 30 in Room 221 of the University of Illinois College of Medicine. His subject will be "The Hardy Pioneer: How He Lived in the Early Middle West." This lecture series was established by friends and associates of Dr. Davis on his retirement as dean of the College of Medicine in 1943.

Appoint Assistant Dean.—Dr. Milan V. Novak, a member of the faculty of the College of Medicine since 1940, has been appointed assistant dean of the Graduate College for the University of Illinois' Chicago Professional Colleges. He will continue to serve also as head of the department of bacteriology. He will be in charge of administrative duties for the Graduate College on the campus of the Chicago Professional Colleges. The new position has been created by the university because of the increase in enrolment of graduate students, together with the need for expediting routine connected with this work. The number of students enrolled in graduate work on the Chicago campus has tripled since the close of the war.

Cleft Palate Training Center.—Clinical training in the care of children with cleft palate has been established at the University of Illinois. A special clinic for research, diagnosis and follow-up of children with cleft lips and palates is being set up

in the university's Dentistry-Medicine-Pharmacy building. Primary financial support will come from the Children's Bureau of the Federal Security Agency, which has granted $175,000 for a period of four to five years. Herbert K. Baker, Ph.D., professor of audiology and director of speech and hearing rehabilitation in the college of medicine, has been appointed director. The new program will make possible long term follow-up and research in the value of various aspects of the care of cleft palate children.

Welfare Council Asks for Additional Funds.—The Health Division of the Welfare Council of Metropolitan Chicago has appealed to the governor and the legislature to appropriate additional state funds for adequate health protection for the people of Illinois. It was emphasized that this can only be attained through local health departments. The state health department is not equipped to do the thorough job necessary, it was said. The Illinois Department of Public Health has available annually about $4,700,000, of which about $2,000,000 is from federal sources and the balance from state funds. The Chicago Board of Health receives no state funds, according to the council, but has been allotted $543,160 in federal funds through the state department to be used for mental hygiene and tuberculosis and venereal disease control. The Cook County Health Department is receiving $118,657 from the state, and the Evanston Health Department is receiving $34,236. Among deficiencies in health protection for the city, the council listed virtually no health services for nearly 750,000 school children in the city; no health supervision for preschool age children in at least 80 per cent of the city; the need of 100 additional sanitary inspectors; the urgent need of 250 public health nurses, and virtually no public health programs to conserve health through health education, mental hygiene and health services for the aged. California and New York, according to the council, provide grants-in-aid for local health work on a much more liberal basis than Illinois. California distributes $3,000,000 annually and New York provides at least 50 per cent of the funds for local public health work, and in poorer communities up to 75 per cent.

IOWA

Iowa Heart Association.—A group of Iowa physicians recently organized the Iowa Heart Association as an affiliate of the American Heart Association. Dr. Herbert W. Rathe, Waverly, was named president and Dr. Lewis E. January, secretary. Both are faculty members of the State University of Iowa College of Medicine, Iowa City.

State Medical Meeting.—The Iowa State Medical Society will hold its annual session at Hotel Fort Des Moines in Des Moines April 18-21, under the presidency of Dr. William E. Ash, Council Bluffs. Guest speakers at the general sessions include:

Harry H. Gordon, Denver, Problems in the Diagnosis and Treatment of Rheumatic Fever.
Richard B. Cattell, Boston, Inflammatory Lesions of the Small and Large Bowel.
Arthur L. Conrad, J.D., Chicago, Social, Moral and Economic Implications of Political Medicine.
Lawrence R. Boies, Minneapolis, Headache and Neuralgia of Nasal Origin.
Walter H. Nadler, Chicago, Sarcoidosis.
Louis A. Buie, Rochester, Minn., Ulcerative Colitis.
Walter P. Blount, Milwaukee, Fractures in Children Are Different.
Forrester Raine, Milwaukee, Diagnostic Difficulties in Carcinoma of the Lungs.
William F. Mengert, Dallas, Tex., Pelvic Pain in Women.
William A. Boice, Chicago, Indications for Cesarean Section.
Abe B. Baker, Minneapolis, Treatment of Epilepsy by the General Practitioner.
Austin Smith, Secretary, Council on Pharmacy and Chemistry, American Medical Association, Chicago, Food and Drug Act.
Arthur M. Olsen, Rochester, Minn., Differential Diagnosis of the More Common Pulmonary Conditions.

Section meetings on surgery, medicine, pediatrics, obstetrics and eye, ear, nose and throat will be held in the afternoons.

KANSAS

Course in Ophthalmology and Otolaryngology.—The University of Kansas in cooperation with the Kansas Society of Ophthalmology and Otolaryngology, the Kansas Medical Society and the state board of health will present a graduate course in ophthalmology and otolaryngology at the university medical center in Kansas City April 11-15. It is open to any doctor of medicine in the state and adjacent states. Among the instructors will be Drs. Stuart C. Cullen, Iowa City; Frank S. Forman Jr., Kansas City, Mo.; Arthur C. Jones, Boise, Idaho; Albert D. Ruedemann, Detroit, and Benjamin H. Shuster, Philadelphia. A fee of $30 is charged for the full course, $20 for the first three days in otolaryngology only, or for the last two $15. Complimentary enrolment is granted to interns and residents on identification by their hospital superintendents. Registration should be made with the Extension Program in Medicine, University of Kansas Medical Center, Kansas City 3, Kansas.

KENTUCKY

Sigma Xi Lecture.—Dr. Arnold L. Gesell, Yale University, New Haven, Conn., will deliver a lecture, to which the medical profession is invited, on "Human Infancy and the Ontogenesis of Behavior" at Halleck Hall, Louisville, March 22 at 8 p. m.

Personals.—Dr. John H. Blackburn of Bowling Green, who has completed fifty years as a medical practitioner, was guest of honor at a dinner sponsored by the Warren-Edmonson County Medical Society. The dinner was attended by sixty local physicians as well as by doctors from other parts of the state.——Dr. Annie S. Veech is, at her request, resigning as director of the Louisville-Jefferson County Board of Health and will act as associate director and consultant. From 1922 to 1937 Dr. Veech was on the staff of the Kentucky State Department of Health. She organized the first maternal and child health program in the state health department. Dr. Veech was born in Louisville and graduated from Woman's Medical College in Philadelphia.

MASSACHUSETTS

Hospital News.—Tor Court, the 155 acre Salisbury place, was transferred early December to Hillcrest Hospital, Pittsfield. It is the twenty-first Berkshire estate that has passed to an institutional corporation or state ownership.

Medical Alumni Meeting.—The Tufts Medical Alumni Association will hold its annual dinner meeting on April 6 at the Somerset Hotel, Boston. The guest speaker is to be Dr. Leonard A. Scheele, Surgeon General of the U. S. Public Health Service. Other speakers include Leonard Carmichael, LL.D., president of Tufts College, and Dr. Jacob L. Lochner Jr., Albany, N. Y., secretary, New York State Board of Registration in Medicine. Dr. Roy J. Heffernan will preside. The 25 year class will hold its reunion also on this date.

MICHIGAN

Cancer Day in Flint.—The Genesee County Medical Society is sponsoring a state wide conference at its fourth Annual Cancer Day program at Hurley Hospital, Flint, April 13 from 9:30 a. m. to 5 p. m. The program is as follows:

Arthur P. Stout, New York, Role of the Surgical Pathologist in Respect to the Cancer Problem.
Harold W. Dargeon, New York, Cancer in Children.
Thomas E. Jones, Cleveland, Cancer of the Lower Bowel—Present Status of Management.
Norman F. Miller, Ann Arbor, Management of Uterine Cancer.
E. W. Alton Ochsner, New Orleans, Basic Principles in Cancer Management.

NEW JERSEY

Director of Bureau of Laboratories.—The third of six bureau directors to be selected under the reorganization of the State Department of Health is Dr. A. J. Casselman, Camden, who will be director of the Bureau of Laboratories. Dr. Casselman has been associated with the Bureau of Venereal Disease Control since 1919, and has been chief of the division for the last two years. He will plan, organize and direct a central laboratory equipped to perform all laboratory services required by the New Jersey State Department of Health. He is a graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1911.

NEW YORK

Courses in Surgery and Medicine.—Opportunities for postgraduate education in medicine and surgery are available at the Clifton Springs Sanitarium and Clinic at Clifton Springs. Physicians practicing within the region are eligible. The course in medicine, which runs for a period of one to four months, is under the direction of Dr. Bernard A. Watson, director of the Division of Medicine. All fields except brain surgery are available in the course in surgery under the direction of Dr. William C. Eikner, chief of Surgery Service.

Survey of Tuberculosis Hospitalization.—The New York Tuberculosis and Health Association has published a study based on the average year, 1947, when 2,373 tuberculosis patients left New York City hospitals against medical advice and before their disease had been arrested. Nearly half of the tuberculosis patients who "sign out" have open, infectious disease. The cost of caring for a tuberculous patient is estimated at $7.50 per day per patient, the amount paid by the city to private hospitals for such care. On this basis the "sign out" group alone, each patient averaging 365 hospital days, costs $6,531,682.50 per year.

The cost of public relief for the group and their dependents amounted to $2,134,800. Three city institutions and one in New Jersey were the subject of intensive study. There are twenty-one tuberculosis hospitals in the metropolitan area.

Clinic for Corneal Disorders.—A clinic for diagnosis and treatment of corneal disorders has been established at the Manhattan Eye, Ear and Throat Hospital, 210 East 64th Street, New York, as a cooperative undertaking sponsored by the Eye Bank for Sight Restoration and the hospital. The clinic meets at 9:30 a. m. Wednesday mornings. Patients are referred to this clinic from the other eye services of the Manhattan Eye, Ear and Throat Hospital, from other physicians, from public health organizations and from some of the national and state societies for the prevention of blindness. Most of the patients are charity cases and a great portion of the burden of financing is carried by the eye bank.

Personals.—Dr. Harold H. Berman, Ogdensburg, has been appointed director of the Willowbrook State School on Staten Island, the newest state institution for the mentally defective. Dr. Berman has been on the staff of the St. Lawrence State Hospital in Ogdensburg since 1926 and assistant director since 1938. He is a graduate of Tufts College Medical School, Boston, 1925.——Dr. James J. Quinlivan, Albany, has been appointed permanent assistant director of local health administration in the New York State Department of Health's division of local health service. Dr. Quinlivan has served as acting director since last March. He was formerly district health officer at Saranac Lake, Rochester and Amsterdam and a district health officer in Amsterdam and Johnstown.——Dr. George C. Vogt, Binghamton, has been elected chairman of the medical grievance committee of the State Department of Education, replacing Dr. Roy Upham, New York, who is retiring.——Dr. Ruth Gilbert, who has been in charge of the Diagnostic Laboratories, New York State Department of Health, since 1921 retired January 15.——Dr. Robert L. Ellithorp resigned as health commissioner of Gloversville after thirty years of association with the city health department.——Dr. John K. Meneely Jr., who has been on the staff of Albany Hospital and was made medical director there last December, has been appointed assistant dean of Albany Medical College, and Dr. Thomas Hale Jr. has been appointed associate dean. Dr. Meneely received his medical degree from Yale University School of Medicine, New Haven, Conn. Dr. Hale has been assistant dean at the Albany Medical College since 1943.

New York City

Perrin Long to Give Memorial Lecture.—Dr. Perrin H. Long, professor of preventive medicine at Johns Hopkins Hospital, Baltimore, will deliver the third annual Samuel Strausberg Memorial Lecture, sponsored by the Clinical Society of Beth-El Hospital, on April 26, 8:30 p. m. His subject will be "Clinical Use of Aureomycin, Chloromycetin, Polymyxin and Other New Antibiotics." The lecture will be delivered at the Kings County Medical Society Building, 1313 Bedford Avenue, Brooklyn.

Children's Psychiatric Clinic.—A clinic to provide psychiatric counseling and treatment for emotionally disturbed children as well as their parents recently opened in Brooklyn as an adjunct of the Council Child Development Center in Manhattan. It is aimed at helping pre-school-age Brooklyn children. The clinic will operate on a grant received from the New York State Department of Mental Hygiene, consisting of federal funds allocated by the U. S. Public Health Service for the development of community health service for children.

Institute of Cancer Research.—The Columbia-Presbyterian Medical Center is establishing an Institute of Cancer Research to be staffed by cancer specialists. It is being developed primarily to bring about an integration of the activities in numerous medical sciences concerned with cancer research. Two new major cancer units at the center will be completed during 1949 and 1950. Additions are three new floors of cancer research laboratories atop the Vanderbilt Clinic and the Francis Delafield Hospital being erected at the center by the city. Another research division to be included will be the facilities and personnel of the department of cancer research, which was moved to the College of Physicians and Surgeons in 1938 from the Columbia campus on Morningside Heights. Dr. Cushman D. Haagensen, coordinator of cancer teaching at the Columbia University College of Physicians and Surgeons, has been appointed director of the institute. An associate professor of clinical surgery, Dr. Haagensen has had training in cancer as pathologist, surgeon and investigator. He is assistant attending surgeon and assistant surgical pathologist to Presbyterian Hospital. A coordinating committee has been appointed composed of professors and executive officers of the departments of biochemistry, medicine, obstetrics and gynecology, pathology, pharmacology, radiology and surgery.

PENNSYLVANIA

Special Society Meeting.—The annual meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held April 22-24 at the Penn Harris Hotel, Harrisburg. Among the speakers who will present papers are Drs. Albert D. Ruedemann, Detroit; John R. Lindsay, Chicago; Ralph O. Rychener, Memphis, Tenn.; Carlton S. Nash, Rochester, N. Y.; Jay G. Linn, Pittsburgh; Arno E. Town, New York, and George M. Coates, Philadelphia. The meeting will also include a round table discussion on "Headaches" which will include representatives of all major specialties. There will be a study club to discuss "Cataract Problems."

Philadelphia

Alumni Society Opened to Women.—After fifty-seven years of existence as a men's club, the Philadelphia Alumni Society of the medical department of the University of Pennsylvania decided at its annual meeting on February 19 to welcome as members women graduates of the medical department.

Resolution on Local Water Problem.—The Philadelphia County Medical Society has sent a resolution to Mayor Samuel of Philadelphia expressing its concern over the city water supply, which they designated as unpalatable, ill-smelling and not wholly healthful. It urged that Philadelphia take steps to insure its early, complete and lasting correction.

City Health Survey.—A broad survey of the city's medical and health services and needs began February 19 under the sponsorship of the city's department of public health, the City Planning Commission, the Health and Welfare Council, the Philadelphia County Medical and the Dental societies, the Board of Public Education, the Bureau of Municipal Research and others. Dr. William H. Perkins, dean of Jefferson Medical College, is chairman of the executive committee. Every Philadelphia mother of a 1 year old child will be requested to answer a questionnaire covering the type and frequency of prenatal and postnatal medical care that her child received and by whom such care was rendered.

SOUTH CAROLINA

Laboratory for Study of Radioisotopes.—The Medical College of the State of South Carolina, Charleston, has established a laboratory for the study and use of radioisotopes. The laboratory is under the direction of Dr. Robert B. Taft, professor of radiology; the advisory committee consists of Drs. William M. McCord, professor of chemistry, Frederick E. Kredel, professor of surgery, and Theodore G. Bernthal, professor of physiology.

State Health Council Chartered.—The South Carolina Health Council, designed to strengthen and develop a full health program for the state, was granted a charter February 17. Organized in Florence, the council lists Dr. Harold S. Gilmore of Nichols as chairman, M. L. Meadors of Florence, secretary, and R. L. Dougherty of Columbia, treasurer. It will serve as a clearing house on health and medical care problems and programs, will stimulate creation of local health councils and support specific health programs.

TENNESSEE

Dr. Rolfe Honored.—A testimonial assembly was held at the Meharry Medical College, Nashville, Tenn., January 8 to honor Dr. Daniel T. Rolfe, professor of physiology and chairman of the department of physiology and pharmacology at the college. Dr. Rolfe came to Meharry in 1930. When the department of physiology and pharmacology were combined, he was made chairman.

American Museum of Atomic Energy.—The Oak Ridge Institute of Nuclear Studies has established the world's first permanent museum dealing with atomic energy, to be known as the American Museum of Atomic Energy. The exhibit will be open to the public March 19 when the security gates of the town of Oak Ridge are removed and the community adopts a normal residential and business role. The museum will be operated by the institute, a nonprofit educational corporation of nineteen Southern universities which conducts a program of research and training in nuclear sciences under contract with the Atomic Energy Commission. The display will be housed in a 32,000 square foot structure used as a cafeteria during the war. A small admission charge will be made. William G. Pollard, Ph.D., executive director of the institute, said that "the need for broadening our program to include public education has been apparent for some time."

V 1
194

TEXAS

Dallas Health Museum Award.—Nominations for the 1949 Dallas Health Museum award for outstanding contributions to public health in Texas will be accepted until April 15. They should be submitted to the museum, where they will be reviewed by a board of judges appointed by museum officials.

Personal.—Dr. Charles H. Harris of Harris Memorial Methodist Hospital, Fort Worth, was among eight persons who recently were named to membership in the newly established Methodist Hall of Fame in Philanthropy. He received a hand-engrossed membership certificate from the Board of Hospitals and Homes of the Methodist Church. The honor is bestowed for outstanding contribution of time, talent and money to Methodist philanthropic institutions.

GENERAL

Orthopsychiatric Association Meeting.—The American Orthopsychiatric Association will hold its annual meeting at the Hotel Stevens, Chicago, April 4-6, under the presidency of Samuel J. Beck, Ph.D., Chicago. The general session theme will be "Education for Emotional Insight in a World in Crisis."

National Negro Health Week.—The thirty-fifth annual observance of National Negro Health Week has been scheduled for April 3-10 with the objective to "cooperate with your health agencies and your neighbors for better health and sanitation in your community." A day by day schedule of activities has been made up by the U. S. Public Health Service.

Instruction in Standard Nomenclature.—Basic instruction in Standard Nomenclature through lecture and practice will be a major feature of the Institute for Medical Record Librarians at Buck Hill Falls Inn, Buck Hill Falls, Pa., April 4-8. The Pennsylvania Association of Medical Record Librarians and the Hospital Association of Pennsylvania are sponsors.

Mental Hospital Institute.—The American Psychiatric Association is sponsoring a Mental Hospital Institute in Philadelphia April 11-15. In a drive to improve mental hospital services in the United States and Canada, the institute will draw together several hundred professional and lay leaders for an attack on the problem. Enrolment in the institute is open to public and private hospital staff members and to doctors and laymen in the United States and Canada. It will be under the direction of Dr. Daniel Blain, medical director of the association. The fee for the institute is $50.

Society Elections.—The National Society for Medical Research at its recent annual meeting in Chicago reelected two Chicagoans, Anton J. Carlson, Ph.D., president, and Dr. Andrew C. Ivy, secretary-treasurer.——The Mid-South Postgraduate Medical Assembly at its recent annual meeting installed Dr. Hoyt R. Allen of Little Rock, Ark., as president and chose Dr. Julian G. Price, Dyersburg, Tenn., president-elect.——Officers of the South Atlantic Association of Obstetricians and Gynecologists for the year 1949-1950 are Dr. Charles J. Andrews, Norfolk, Va., president; Dr. Lester A. Wilson, Charleston, S. C., president-elect, and Dr. Emmett D. Colvin, Atlanta, Ga., secretary-treasurer. The next annual meeting will be held at the Hotel Roanoke, Roanoke, Va., Feb. 9-11, 1950.

Four Openings for Visiting Professors in Burma.—The Department of State has recently announced four openings under the Fulbright Educational Exchange Program for visiting professors to teach at the Medical College of the University of Rangoon in Burma beginning in July 1949. The openings are for one academic year and include the fields of orthopedic surgery; eye, ear, nose and throat surgery; dentistry, and public health. One opening is also offered for advanced research in public health. A grant payable in Burmese currency is offered in connection with each opening. Each grant includes stipend, round trip transportation, a maintenance allowance and an allowance for books or equipment essential to the assignment. Requests for further information should be addressed to the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Avenue, Washington 25, D. C.

Meeting on Voluntary Medical Care.—The Council of the New England State Medical Societies will hold a meeting March 27 beginning at 1:30 p. m. at the Copley Plaza, Boston, on voluntary medical care plans in the region. County medical society officers and committee members are also invited to the meeting. Delegates from the six state members will report on "Extending Medical Care in New England through Medical Society Sponsored Voluntary Plans." Mr. Henry D. Locke, research director, Liberty Mutual Insurance Company, Boston, will speak on extending medical care through insurance company programs. Discussion will follow. The meeting will open with a discussion of the national education campaign of the American Medical Association by Mr. Clem Whitaker, campaign director and Leone Baxter, general manager of the campaign. Dr. James R. Miller, Hartford, Conn., will speak on "The Special A. M. A. Assessment."

Dr. Diamond Named Medical Director of Red Cross Blood Program.—At the request of the Committee on Medical Sciences of the Research and Development Board of the National Military Establishment under the auspices of the National Research Council, the National Institutes of Health and the American Red Cross, many researchers in the fields of preservation and use of blood and blood derivatives met recently at the Harvard Medical School in Boston. Particularly stressed were the new developments in the collection, preservation and administration of whole blood and its component parts. The discussions brought out that the American Red Cross, through its National Blood Program, is in excellent position to put into practice many of the recommendations made by medical scientists in this field.

Dr. Louis K. Diamond of Boston has been appointed medical director of the Red Cross National Blood Program. He will be on temporary leave of absence from the Children's Medical Center, Boston, and the department of pediatrics at Harvard Medical School while serving in his new capacity. Dr. Diamond was an investigator dealing with blood transfusion problems for the National Research Council during the war. He has been director of several blood banks and of the Blood Grouping Laboratory of Boston.

Conference on the Nervous System.—A conference on development, growth and regeneration of the nervous system is to be held by the International Union of Biological Sciences at the University of Chicago, March 21-25. A final summary meeting on March 25 will be open to all interested scientists. Subjects to be discussed include differentiation of the central nervous system, nerve fiber orientation and patterns, physiology of neuron growth, peripheral and central nerve regeneration, problems of specificity and selectivity and neural growth and the development of behavior.

Foreign participants in the meeting, which is sponsored by UNESCO and the Rockefeller Foundation, are J. Boeke, Utrecht; Holger Hyden, Stockholm; Rita Levi-Montalcini, Torino; Alberto Stefanelli, Rome; Sydney Sunderland, Melbourne, and John Z. Young, London. American members taking part are D. H. Barron, Ph.D., Yale University, New Haven; David Bodian, Johns Hopkins University, Baltimore; Samuel R. Detwiler, Ph.D., Columbia University, New York; Dr. Louis B. Flexner, Carnegie Institution, Baltimore; Dr. Ralph W. Gerard, University of Chicago; Viktor Hamburger, Ph.D., Washington University, St. Louis; Davenport Hooker, Sc.D., University of Pittsburgh; Dr. Warren H. Lewis, Wistar Institute, Philadelphia; Francis O. Schmitt, Ph.D., Massachusetts Institute of Technology, Cambridge; Carl C. Speidel, Sc.D., University of Virginia, Charlottesville; Roger W. Sperry, Ph.D., University of Chicago; Paul A. Weiss, Ph.D., University of Chicago, and William F. Windle, Sc.D., University of Pennsylvania.

Marriages

JOHN WILLIAM HILLMAN, Emory, Va., to Miss Virginia Swindler of Springfield, Mo., in Baltimore, January 16.

WILLIAM GETZ THUSS JR., Birmingham, Ala., to Miss Gene Bradley Connell of Chattanooga, Tenn., January 22.

HERMAN WINKELMAN, Scotia, N. Y., to Miss Phyllis Wheeler of Cobleskill, in Elmira, December 24.

HARRISON J. BROWNLEE, Pierrepont Manor, N. Y., to Miss Anne Sutton McNeil of Dallas, Pa., October 30.

JOHN F. LEWIS JR., Hoboken, N. J., to Miss Margaret June Murphy in Union City, N. J., January 22.

ALFRED GUERIN ALLEN, San Francisco, to Miss Cora Elizabeth Robinson of Churchill, Md., recently.

BILLY BOOTH BRINKLEY, Bristol, Tenn., to Miss Sarah Eunice Legate at Lexington, Miss., January 16.

CLARENCE F. WEBB, Grand Rapids, Mich., to Miss Maxine Mueller, in Dwight, Ill., recently.

SAMUEL L. PARKER JR., to Miss Frances Carr, both of Durham, N. C., recently.

FRANCIS PHILIP BILELLO to Miss Jeanne Grace Liota, both of Brooklyn, January 9.

Deaths

John Bramwell Davis, Denver; born in Indianapolis, Nov. 4, 1874; Gross Medical College, Denver, 1902; past president of the Denver Clinical and Pathological Society; member of the American Medical Association; member of the American Urological Association and past president of the South Central Section; fellow of the American College of Surgeons; formerly on the faculty of the University of Colorado School of Medicine; specialist certified by the American Board of Urology, Inc.; served as a member and secretary-treasurer of the state board of medical examiners; consulting urologist for Selective Service during World Wars I and II; affiliated with the Denver and Colorado general hospitals, Children's Hospital, Mercy Hospital and St. Luke's Hospital, where he died December 23, aged 74, of pulmonary edema.

Basil R. Beltran ✙ Philadelphia; born in New Orleans in 1889; Medico-Chirurgical College of Philadelphia, 1912; associate professor of surgery at the Medico-Chirurgical College, Graduate School of Medicine, University of Pennsylvania; received the Palme-Academie decoration of the Ministry of National Education of France for services rendered to the French during World War I and to the French in Philadelphia; served as medical director and chief surgeon of the Eastern State Penitentiary, chief and chairman of the staff of the Nazareth Hospital; affiliated with the Misericordia and Fitzgerald Mercy hospitals; died January 19, aged 59, of hypertension and cardiac failure.

Louis Rudolph ✙ Chicago; born in Racine, Wis., in 1886; Northwestern University Medical School, Chicago, 1911; specialist certified by the American Board of Obstetrics and Gynecology, Inc.; member of the Central Association of Obstetricians and Gynecologists and Chicago Gynecological Society; fellow of the American College of Surgeons; served on the faculty of Loyola University School of Medicine; professor of obstetrics at Cook County Graduate School of Medicine; affiliated with Mount Sinai and Cook County hospitals; died in Wesley Memorial Hospital January 29, aged 63, of acute hepatitis and acute pancreatitis.

Kasimir Ambrose Zurawski, Chicago; born in Poland Dec. 20, 1871; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1899; in 1913 member of the House of Delegates of the American Medical Association; at one time on the faculty of his alma mater; spent several years in Poland improving health conditions in that country and served as minister of health under the Pilsudzki government; decorated by the Polish government and awarded an honorary degree by the University of Warsaw; died in St. Luke's Hospital January 24, aged 77.

Paul Appleton ✙ Providence, R. I.; Harvard Medical School, Boston, 1915; specialist certified by the American Board of Obstetrics and Gynecology; member of the New England Obstetrical and Gynecological Society; fellow of the American College of Surgeons; served during World War I; on the staff of the Providence Lying-in Hospital; died December 24, aged 61, of myocardial infarction.

Joseph Henry Cahoon, Middletown, Del.; University of Maryland School of Medicine, Baltimore, 1903; died in the Delaware Hospital December 12, aged 83, of arteriosclerosis.

Hanna L. Caldwell, Miami, Fla.; Bennett Medical College, Chicago, 1904; died December 6, aged 79.

Miles Dudley Chisholm ✙ Westfield, Mass.; University College of Medicine, Richmond, 1900; fellow of the American College of Surgeons; served during World War I; formerly city physician; served on the staff of the Noble Hospital; died December 19, aged 71, of coronary disease.

Herman Vascoe Collins, Monroe, La.; Atlanta School of Medicine, 1911; member of the American Medical Association; died December 2, aged 66, of carcinoma of the small intestine.

Perry E. Cotton ✙ Elwood, Ind.; Indiana University School of Medicine, Indianapolis, 1934; died November 29, aged 40, of injuries received when the automobile in which he was driving was struck by a train.

Charles Wellington Craik, Venice, Calif.; University Medical College of Kansas City, 1900; served during World War I; died in the Veterans Administration Center, Los Angeles, in December, aged 76.

Hugh G. Dallas, Jefferson City, Mo.; St. Louis College of Physicians and Surgeons, 1908; died in St. Mary's Hospital December 8, aged 65.

Emory Francis Davis, Springfield, Ohio; Medical College of Ohio, Cincinnati, 1897; member of the American Medical Association; died December 25, aged 78, of pulmonary embolism and carcinoma of the cecum.

John Diven ✙ Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1912; died in Wilmington, Del., December 16, aged 65.

Monica Donovan ✙ San Francisco; Stanford University School of Medicine, San Francisco, 1917; member of the American Roentgen Ray Society and of the Radiological Society of North America; formerly on the faculty of her alma mater; medical advisor to the San Francisco College for Women; affiliated with St. Mary's Hospital; died December 29, aged 57.

Theodore Jordan Drisdel, Greenfield, Mo.; St. Louis University School of Medicine, 1905; served during World War I; died December 7, aged 68, of heart disease.

Fred Conrad Enander ✙ New Britain, Conn.; Tufts College Medical School, Boston, 1922; died December 21, aged 51.

Julius Ernest Fleischner ✙ Chicago; University of Illinois College of Medicine, Chicago, 1923; served during World War I; affiliated with the Loretto and Garfield Park Community hospitals; died in River Forest, Ill., December 26, aged 51, of arteriosclerotic heart disease.

Gustav Adolphus Floreth ✙ Mount Olive, Ill.; Marion-Sims-Beaumont Medical College, St. Louis, 1903; served overseas during World War I; for many years member of the board of education; died December 23, aged 71, of coronary thrombosis.

Gilbert E. Frank, Harbor Springs, Mich.; Detroit College of Medicine, 1901; member of the American Medical Association; died in St. Johns, December 20, aged 69, of lymphosarcoma.

Christopher C. Gaard ✙ Bremerton, Wash.; St. Louis University School of Medicine, 1920; died in the Harrison Memorial Hospital December 16, aged 60, of carcinomatosis.

Parker Blair Gamble, Detroit; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1913; member of the American Medical Association; served on the staff of Parkside Hospital; died December 27, aged 62, of coronary thrombosis, hypertension and arteriosclerosis.

Leroy Clarence Green, Ashville, N. Y.; University of Buffalo School of Medicine, 1895; member of the American Medical Association; since 1919 health officer of the town of North Harmony; died December 29, aged 77, of paralysis agitans.

Francis Preston Gudgell, Owingsville, Ky.; University of Louisville Medical Department, 1882; member of the American Medical Association; died in the Good Samaritan Hospital, Lexington, December 23, aged 88.

Erwin Kroll Gutmann, Jersey City, N. J.; Cornell University Medical College, New York, 1929; member of the American Medical Association; served overseas during World War II; died December 21, aged 44, of coronary thrombosis.

Tryggve Alexander Hagerup, Dodgeville, Wis.; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1920; member of the American Medical Association; past president of the Iowa County Medical Society; died December 17, aged 55, of acute atrophy of the liver.

Robert Clarence Hannigen, Amesbury, Mass.; Medical School of Maine, Portland, 1901; member of the American Medical Association; served during World War I; died in the Amesbury Hospital December 16, aged 71, of cerebral thrombosis.

Hugh Henry Hanrahan ✙ Rutland, Vt.; University of Vermont College of Medicine, Burlington, 1915; died December 14, aged 61, of myocarditis.

Hiram Abiff Haskell, Windsor, Calif.; Northwestern University Medical School, Chicago, 1899; served with the British Army during World War I; died December 25, aged 86, of injuries received when struck by an automobile.

Carl John Hawley ✙ Burbank, Calif.; University of Southern California School of Medicine, Los Angeles, 1935; served during World War II; died in the Veterans Administration Hospital, Van Nuys, December 26, aged 44, of hypertension and cerebral hemorrhage.

Ralph H. Herbert, La Crosse, Wis.; Bennett Medical College, Chicago, 1900; died in La Crosse Hospital, December 24, aged 70, of cerebral hemorrhage.

Frank McElroy Huntoon, Syracuse, N. Y.; Cornell University Medical College, New York, 1903; member of the Society of American Bacteriologists; formerly on the faculty of his alma mater; at one time senior bacteriologist and medical director, H. K. Mulford Company in Glen Olden,

Pa.; served during World War I; died in the Onondaga Sanatarium, December 21, aged 67, of pulmonary tuberculosis.

Alfred Edward Jones, Chicago; University of Illinois College of Medicine, Chicago, 1915; member of the American Urological Association; fellow of the American College of Surgeons; specialist certified by the American Board of Urology; formerly on the faculty of Loyola University School of Medicine; served during World War II; affiliated with Michael Reese Hospital; died November 10, aged 58, of chronic myocarditis.

Weston William Lasher, Saxonburg, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1893; member of the American Association of Industrial Physicians and Surgeons; died in the Allegheny Valley Hospital, Tarentum, December 12, aged 77, of leukemia.

Leonard Frank Lauf, Columbus, Ohio; Jefferson Medical College of Philadelphia, 1907; member of the American Medical Association; died December 16, aged 65, of hypertension.

Hugh Francis Lena ✠ New London, Conn.; Johns Hopkins University School of Medicine, Baltimore, 1916; past president of the New London County Medical Society; fellow of the American College of Surgeons; served during World War I; owner of Dr. Lena's Surgical Hospital; died November 8, aged 60, of coronary occlusion.

Roy Chester Lowe, Neenah, Wis.; the Hahnemann Medical College and Hospital, Chicago, 1906; member of the American Medical Association; past president of the Winnebago County Medical Society; died in the Theda Clark Hospital December 16, aged 65.

William Douglas Macon, Charlottesville, Va.; University of Virginia Department of Medicine, Charlottesville, 1897; member of the American Medical Association; resigned in 1924 as professor of obstetrics at his alma mater, where he had been clinical instructor in anesthesia in 1904 and in the following year also in the practice of medicine; served as health officer for the city of Charlottesville; died December 30, aged 79, of carcinoma.

Fred E. Murphy, Traverse City, Mich.; Detroit College of Medicine, 1906; died in the University Hospital, Ann Arbor, December 1, aged 71, of carcinoma of the pancreas with metastases.

Clyde Clark Neese ✠ Wilmington, Del.; Temple University School of Medicine, Philadelphia, 1917; member of American Proctological Society; served during World War I; died in the Wilmington General Hospital December 5, aged 60, of congestive heart disease.

David Stanislaus O'Donnell, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia 1905; served during World War I; affiliated with St. Joseph's Hospital, where he died December 23, aged 68.

John Joseph O'Loughlin, Howard Beach, N. Y.; Fordham University School of Medicine, New York, 1918; served during World War I; member of the American Medical Association; died December 14, aged 55, of cerebral hemorrhage.

William Robert Orr, Helena, Ark.; Tulane University of Louisiana School of Medicine, New Orleans, 1908; died in Helena Hospital December 1, aged 65, of injuries received in an explosion on a river cruiser.

Michelangelo Pacella, Waukegan, Ill.; Chicago Medical School, 1922; died in St. Theresa Hospital December 11, aged 78, of chronic nephritis and pneumonia.

Lovick Edward Peacock, West Blocton, Ala.; Medical College of Alabama, Mobile, 1892; member of the American Medical Association; died December 23, aged 78, of bronchogenic carcinoma.

Edward August Peterson, Vallejo, Calif.; Medical Department of the University of California, San Francisco, 1907; served overseas during World War I; formerly on the staff of Vallejo General Hospital; died in Napa, December 9, aged 67, of heart disease.

Austin Flint Philpott, Fort Madison, Iowa; St. Louis College of Physicians and Surgeons, 1903; died in the Sacred Heart Hospital December 20, aged 67, of chronic nephritis.

Theodore A. Pierson, Hopewell, N. J.; College of Physicians and Surgeons, Baltimore, 1894; member of the American Medical Association; served three terms as mayor of Hopewell and as president of the board of education; director of the Hopewell National Bank; died December 24, aged 78, of gallbladder disease.

Pierre Celestin Pilon, Minneapolis; School of Medicine and Surgery of Montreal, Canada, 1886; served during World I; formerly mayor of Paynesville and coroner of Stearns County; died in St. Mary's Hospital December 16, aged 84.

Lewis R. Polk ✠ Memphis, Tenn.; Memphis Hospital Medical College, 1909; died December 18, aged 63, of cerebral hemorrhage and hypertension.

Lorne McDonnell Ryan, Madison, Conn.; McGill University Faculty of Medicine, Montreal, Canada, 1905; member of the American Medical Association and of the Medical Society of the State of New York; fellow of the American College of Surgeons; affiliated with St. Peter's Hospital in Brooklyn; consulting surgeon to St. Anthony's Hospital in Woodhaven, N. Y.; died December 30, aged 67, of coronary thrombosis.

Raymond St. Clair, Sonoma, Calif.; College of Physicians and Surgeons, Keokuk, Iowa, 1896; past president of the Nevada State Medical Association; died November 30, aged 78.

Michael Abdallah Saleeby, Dillon, S. C.; Medical College of the State of South Carolina, Charleston, 1917; died in the McLeod Infirmary, Florence, December 29, aged 55, of coronary thrombosis.

Walter Howard Sanford, New York; Albany (N. Y.) Medical College, 1899; recently retired as pathologist at the Manhattan State Hospital; died December 13, aged 70, of angina pectoris.

Preston Pope Satterwhite, Great Neck, N. Y.; Bellevue Hospital Medical College, New York, 1898; died in the Harkness Pavilion, New York, December 27, aged 80.

Abe Lewis Scheff, Birmingham, Ala.; Vanderbilt University School of Medicine, Nashville, Tenn., 1916; served during World Wars I and II; formerly passed assistant surgeon in the U. S. Public Health Service, reserves; at one time director of the Santa Cruz (Ariz.) Health Service; affiliated with the Veterans Administration; died December 17, aged 54, of coronary thrombosis.

Harry M. Schuffell ✠ Canton, Ohio; Western Reserve University Medical Department, Cleveland, 1893; fellow of the American College of Surgeons; specialist certified by the American Board of Surgery; consulting surgeon at the Mercy Hospital, where he was chief of staff for many years; on the medical board of the Aultman Hospital; died in Orlando, Fla., December 22, aged 82, of arteriosclerotic heart disease.

Mosé Scuccimarra, Peekskill, N. Y.; Fordham University School of Medicine, New York, 1919; member of the American Medical Association; examining physician for the Selective Service Board during World War II; died in the Memorial Hospital, New York, December 26, aged 65.

Zebidee Lafayett Shipley, Cookeville, Tenn.; Chattanooga Medical College, 1902; member of the American Medical Association; died November 14, aged 75, of cerebral thrombosis.

James H. Shipper, Martinsburg, W. Va.; Baltimore University School of Medicine, 1897; at one time member of the state board of health and city and county health officer; affiliated with the City Hospital and the King's Daughters' Hospital, where he died December 27, aged 84, of paralysis.

James Edward Smith ✠ Rolla, Mo.; Tulane University of Louisiana School of Medicine, New Orleans, 1912; formerly associated with the U. S. Public Health Service; served as medical officer in charge of the U. S. Trachoma Hospital in Knoxville, Tenn., and the Missouri Trachoma Hospital in Rolla; died December 1, aged 60.

Don Carlos Stansberry, Hastings, Neb.; College Physicians and Surgeons, Keokuk, Iowa, 1890; died December 25, aged 87.

Samuel Cecil Stanton ✠ Chicago; Northwestern University Medical School, Chicago, 1892; an Affiliate Fellow of the American Medical Association; served during the Spanish-American War and World War I; formerly consulting medical director of the Federal Reserve Life Insurance Company and medical director of the Farmers National Life Insurance Company of America; died January 26, aged 92, of cerebral thrombosis and diabetes mellitus.

Jacob Erhard Steimen, Boston; College of Physicians and Surgeons, Boston, 1907; died November 15, aged 76, of coronary occlusion.

David Thomson ✠ Burbank, Calif.; Rush Medical College, Chicago, 1914; affiliated with the Physicians and Surgeons Hospital in Glendale; died recently, aged 65, of coronary occlusion.

Sara Elise Wise, Los Angeles; Hahnemann Hospital College of San Francisco, 1893; College of Physicians and Surgeons, Boston, 1894; died in December, aged 83.

Foreign Letters

PARIS

(From a Special Correspondent)

Feb. 5, 1949.

Research in French Universities

ANTIHISTAMINES

B. N. Halpern, who studied the first antihistamine substance used therapeutically (antergan® [dimethylamino-ethyl benzylaniline]) is still actively working on this subject. With his collaborator, Reber, he has just discovered a phenomenon of which the practical consequences have not yet been appreciated. The edema of local infection, provoked in the body of an animal by subcutaneous injection of Salmonella typhimurium or of Staphylococcus, is inhibited by certain antihistamines such as "phenergan." There is a remarkable contrast between such animals treated or not treated by the antihistamine substance: (*a*) in animals infected with subcutaneous injection of the aforementioned germs, but without "phenergan," no deaths occurred; (*b*) in 80 per cent of animals infected in the same conditions and treated with "phenergan" complications developed, septicemia and visceral abscesses, which terminated in death. It is assumed that these complications occurred because the antihistamine in preventing local edema thus destroyed a natural barrier to the diffusion of the infection through the bodies of the experimental animals. The important question—because of these results—is whether antihistamine substances are contraindicated during the development of local infections in man.

LEUKEMIA

Leukemia is being made the subject of vigorous active research. The cytologic studies undertaken particularly (among others) by Bessis and Dreyfus (Bessis, M.: Cytologic sanguine normale et pathologique, Paris, Mason & Cie., 1948; Bessis, M., and Dreyfus, B.: *Semaine d. hôp. Paris* **24**: 1739, 1948) have focused attention on two fundamental characteristics of the leukemic cells: (*a*) the phenomena of arrest of cellular maturation, and (*b*) the sudden appearance of more and more young forms in the developmental course of the disease; these characteristics are common to both cells of leukemia and sarcomatous cells. From a therapeutic point of view, the "exsanguinotransfusions" (Bernard, J., and Bessis, M.: *Bull. et mem. Soc. med. Paris* **64**: 14, 1948) as well as large and repeated transfusions (Vallery-Radot; Hamburger, J.; Milliez, P.; Domart, A.; Dreyfus, B., and Barbizet, J.: *Semaine d. hôp. Paris* **24**: 1979, 1948) are capable of causing remissions of great theoretic interest, for they suggest the existence of antileukemic elements in the blood of normal persons.

ARTERITIS

The treatment of arteritis of the lower limbs by the intra-arterial injections of oxygen is being made the object of research by Lemaire, Loeper and Housset (Lemaire, A.; Loeper, J., and Housset, E., in Journées Therapeutiques de 1948, to be published). These workers administered 70 to 100 cc. of oxygen at each sitting under a pressure represented by the midpoint between the maximum and minimum arterial pressures. The treatment must be used exclusively for the lower limbs. The functional results, represented by a lessening or disappearance of intermittent claudication, appear generally good. The relieving of pain on walking, standing, etc., is of longer duration than that obtained by the traditional methods of treatment.

THE NETHERLANDS

(From Our Regular Correspondent)

AMSTERDAM, Feb. 21, 1949.

Rubella Teamwork in Holland

Shortly after the war, in a scientific meeting sponsored by the *Nederlandsch Tijdschrift voor Geneeskunde*, Professor van Gilse, otologist in the University of Leyden, spoke about rubella and congenital anomalies.

During the war foreign literature was extremely rare in Holland, so that it was not until after the liberation that a copy of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION containing an article by Albaugh (Nov. 10, 1945, p. 719) brought insight into the combination of anomalies of a patient seen by the ophthalmologist Professor van der Hoeve and Professor van Gilse: cataract of the lens in one eye, pigment anomalies in the retina of the other eye, total deafness, anomaly of the heart and mental deficiency.

Soon after this first experience and well informed meanwhile by the literature that had appeared since the first publications of Gregg (1941, 1942) a working group started studying the problem in the Netherlands. Many data were collected by the inquiries of Miss E. Kamerbeek, school physician (Rotterdam), in the five Netherland institutions for the deaf and dumb and afterward among specialists all over the country.

Till now, Professor van Gilse's team has studied in Holland 124 cases of congenital anomalies in children whose mothers suffered from a rubella infection during the first months of pregnancy; 52 patients were registered by ophthalmologists (41 of them were operated on for cataract by Professor Weve, Utrecht), and 34 were found in the schools for deaf and dumb.

The team gave attention to the many sides of the problem. The virus work was done under the auspices of the Institute of Preventive Medicine at Leyden (Prof. J. P. Bijl and Prof. J. D. Verlinde). Attempts to obtain the virus have not been successful, and the infection of monkeys also failed.

Hildernisse and Verlinde without success repeated the work of Steinmaurer (Vienna), who believes that he has followed the development of the virus in the body by means of the electron microscope. They confirmed the specific phenomenon of the intracutaneous injection of convalescent serum during the incubation period: no exanthem occurred on the spot of the injection.

In accordance with Möschlin (Zürich), great value was attached to the presence of "plasma cells" in the blood. The hematologist S. J. de Vries (Amsterdam), and also Rietra (Amsterdam), called attention to the fact that there is no common opinion on the significance of the "plasma cells" or "pathologic lymphocytes." However, the impression of the members of the research team is that one does well to give adequate importance to the results of the blood examination along with other criteria. These pathologic blood elements occur in increasing numbers during the first days after the eruption of the exanthem. In 1 case of a tonsillectomy on the day when rubella appeared, the pathologist Miss van Beek (Leyden) found a layer of plasma cells under the epithelium of the tonsils.

Administration of convalescent serum or specific globulin was stated to be the only prophylaxis today, besides promoting rubella in as many young girls as possible. In this country the induced abortion is mostly rejected for ethical-religious as well as for practical reasons: The 100 per cent anomalies in case of rubella in the first two months of pregnancy are not as

absolutely certain as was stated in the first Australian publications. One does not know to what extent the anomalies will appear. Cataract may be operated on with success. For deaf children possibilities exist of making suffering bearable.

Attempts to infect adults in order to obtain serum have failed. On the other hand, the State Institute, the Central Blood Transfusion Service of the Red Cross, the Health Services of Amsterdam and Rotterdam and many provincial centers are cooperating in the gathering of convalescent serum. Appeals to the general practitioners are also regularly made in the medical periodicals. In all the cases of pregnant women who in the first months had been likely to be infected with rubella and had been given injections during the supposed incubation period, the disease did not appear; the children born were healthy. Cases in which the convalescent serum was given in the beginning of the disease have not been recorded.

ITALY

(From Our Regular Correspondent)

FLORENCE, Jan. 25, 1949.

National Surgical Association

The fiftieth Congress of the Italian National Surgical Association was held in Bologna last October, contemporaneously with the Congress of Internal Medicine. The first subject, "Visceral Pain," was reported on in a previous letter. The second subject was "Surgery of the Vagus." The speaker, Professor Pieri, Rome, discussed the clinical indications of vagotomy based on observations in 151 patients operated on; vagotomy was performed on 142 patients and resection of the branches of the vagus on 9 patients. Good results were obtained with vagotomy in neuralgia of the vagus, in bronchial asthma and in gastric neurosis. Tuberculous laryngitis provided good indications for resection of the superior laryngeal nerve, but this method is now surpassed by the treatment with streptomycin and aerosols. Results were not satisfactory in toxic diffuse goiter, cardiospasm and cancer of the esophagus.

In 1927 Professor Pieri suggested vagotomy as a method of treatment for peptic ulcer, a suggestion based on the belief that the process of autodigestion of the gastric mucosa may result from a functional lack of equilibrium of the innervation of the stomach, with the vagal effects prevailing. This method, however, was not practiced at this time; it was only in 1943, after the reintroduction by Dragstedt, that vagotomy was practiced on a large scale. In 130 cases of vagotomy, on which the speaker's experience is based, results always were fairly satisfactory, although it has not yet been possible to pass final judgment. Today one can state that vagotomy is indicated in recurrences of peptic ulcer, in high gastric ulcers and in duodenal ulcers. Vagotomy, as a rule, should be combined with gastroenterostomy. Concerning the technic the speaker favors subdiaphragmatic vagotomy for gastric neuroses and peptic ulcers. The mortality rate is 3.3 per cent.

Those who participated in the discussion which followed the report were in favor of vagotomy when it is indicated. Professor Dogliotti, of the University of Turin, was in favor of subdiaphragmatic vagotomy for gastroduodenal ulcers, on the basis of his own 70 cases. He suggested calling vagotomy "Pieri's operation" in honor of the surgeon who first conceived and applied it.

The third subject of the Congress was "Postoperative Tetanus." The speaker, Professor Giovannini from Bologna, started from the premise that, notwithstanding the most careful asepsis before and during surgical intervention, there may still be observed cases of postoperative tetanus; i. e., those which occur after surgical intervention carried out with due precautions in an area which has not been infected with Clostridium tetani during recent trauma. The pathogenesis constitutes the central problem of the question. The exogenic origin of tetanus was demonstrated in some cases (use of contaminated material or improperly sterilized instruments). The part which surgical gut may play in the occurrence of tetanus in these cases has been exaggerated. The preoperative iodinization, however, of the surgical gut according to suitable standards is a satisfactory prophylactic safeguard against the tetanus germ.

One must admit that in many cases the tetanus is of endogenous origin. The surgical intervention provides for the germ, a saprophyte already present in the organism, the optimum local and general conditions under which it may develop. In a few cases one may admit that tetanus has been present before the intervention and that it was manifested clinically only after the intervention.

Specific prophylaxis consists of simultaneous injections of serum and anatoxin in different areas; these should be repeated conveniently. The most rational treatment consists of serum-anatoxin therapy by any route according to the preference of the individual surgeon. Curare is a useful sedative for the muscles. Penicillin is effective. The mortality from postoperative tetanus still varies from 50 to 70 per cent.

The fourth subject on which reports were made was "Anesthesia by Endotracheal Intubation" and "Curare in Anesthesia." The subject was divided in two parts. The first part ("Endotracheal Anesthesia") was presented by Dr. Cura and Dr. Manzocchi from Milan, who affirmed that the adoption of the endotracheal technic in the field of inhalation narcosis constitutes the realization of one of the most important advances in the realm of anesthesia.

One speaks of endotracheal anesthesia by means of insufflation when the anesthetic mixture is introduced into the lungs under positive pressure; on the contrary one speaks of endotracheal anesthesia by means of inhalation when the anesthetic mixture is inhaled and exhaled by means of an endotracheal catheter with atmospheric pressure; the latter today is the technic almost universally adopted.

After a description of the instrumentarium (Magill's tube, laryngoscope, Magill's forceps, nebulizer) the speakers discussed the technic of intubation of the trachea; they emphasized that it should be carried out rapidly and without trauma. Muscular relaxation and absence of reflexes are essential for preventing complications. If one wants to follow the orotracheal route the position of the patient represents the most important technical detail; Chevalier Jackson's second position should be preferred. If one wants to follow the rhinotracheal route, tubular breathing is to be considered the safest guide on the progress of the tube toward the vocal glottis; it increases as it gets nearer to the glottis and it remains as such when the tube is inside the trachea. Trauma must be avoided during the removal of the tube, and it seems convenient to perform extubation with the patient under anesthesia.

Concerning the methods of anesthesia under which intubation may be carried out, the speakers stated that after appropriate preanesthesia intubation may be performed with patient under general or local anesthesia. The speakers then listed many advantages of the endotracheal method as compared with other methods of anesthesia by inhalation, and they also mentioned a few disadvantages.

The second part of the reports was devoted to "Curare in Anesthesia." Professor Tosatti from Rome presented the history of the pharmacology of curare, and in addition its effect on man and its employment for the practice of anesthesia.

Correspondence

THE TOWN MEETING DISCUSSION OF COMPULSORY SICKNESS INSURANCE

To the Editor:—If the public had any impression that Mr. Ewing and the proponents of compulsory sickness insurance are waging a clean fight based on sound fact, the recent debate at the Town Meeting of the Air, in Town Hall, New York, should dispel such naive thinking. The attack is now concentrated on the profession of America as represented by the American Medical Association and the 85 per cent of American physicians who are determined to save the American people from the catastrophe of federalized control of the private practice of medicine.

The Utopian promises are made of free medicine (of course of the highest order!), plenty of doctors, plenty of nurses, hospitals and equipment, accelerated research in a dreamland free from disease, human error and suffering, all for 75 cents a week per person. The American Medical Association was charged with hiding behind an "Iron Curtain" through which the public may not penetrate and behind which its members cannot be heard.

A carefully planned trick of planting a question based on the protest of 136 uninformed members of the American Medical Association was used to permit Mr. Cruikshank of the American Federation of Labor to charge that the doctors are held behind this "Iron Curtain" to prevent them from supporting compulsory sickness insurance. Mr. Ewing and Mr. Cruikshank do not seem to know that the House of Delegates is made up of freely elected delegates from the state societies. All the freedom of a true democracy is the fundamental right of every member of the American Medical Association. Any charge to the contrary springs from ignorance of the functions and operations of our House of Delegates.

It was obvious by the character of the planted questions at this forum that the intent is now to "divide and conquer." The attack is being concentrated on the responsible, elected leaders of the American Medical Association for one purpose and one purpose only. It is to cause dissension in our ranks. This has become a vicious fight. If ever the American medical profession needed solidarity it is now. Forget petty differences and let us show the people that we are fighting to protect them from all the evils of political medicine. Let us not be drawn into the trap being set by those who would capitalize on the defections of a few.

F. F. Borzell, M.D.,
Speaker of the House of Delegates, Philadelphia.

PHYSICIANS FOR THE ARMED FORCES

To the Editor:—In regard to your Current Comment headed "Drive To Obtain Physicians For The Armed Forces Recommended," in The Journal, February 12, I should like to offer the following suggestions:

1. Service should be compulsory in the armed forces for all A.S.T.P. and Navy V-12 students who secured their medical education at government expense and who for various reasons were discharged from the services when their medical education was completed; they should now be made to give the two year period that other men who were not discharged have been giving.

2. Those men of military age (to 60 years) who did not serve in the armed forces in World War II by reason of "essentiality" or physical reasons, dependents (the United States considers an army officer's pay sufficient to keep a family) or who were able to ignore the war and go about their own interests, should be inducted and "allowed" to do their bit for two years. This class would secure the needed specialist care that the armed forces lack.

It should be borne in mind that a man up to the age of 60 who is able to practice in civilian life is able to serve his country in time of peace. The younger men can serve in the more active assignments, the older men in hospitals, dispensaries, recruiting, sea assignments on larger ships.

Proper regulations can readily be made that will provide physical examinations and records that will prevent those serving in these two classes from securing a retirement for disability that is not a legitimate claim from service acquired injury or illness.

If this plan should be followed there would be no shortage of physicians in the armed forces.

Robert John Carpenter, M.D.
North Adams, Mass.

REPORTS OF MEDICAL EXAMINATIONS FOR VETERANS ADMINISTRATION RATING AGENCIES

To the Editor:—The National Rehabilitation Commission of the American Legion wishes to call to the attention of the medical profession that many veterans who are attempting to get disability claims adjudicated before Veterans Administration rating agencies are experiencing delays and handicaps in accomplishment of final rating because of physicians' reports and statements which are unsatisfactory or not acceptable to the Veterans Administration for one reason or another. The purpose of this statement is to clarify what the Veterans Administration desires of physicians' reports to adjudicate claims properly. The Veterans Administration regulations require that the physician's statement be notarized only in initial establishment of service connection for a specific disease or condition. While this requirement is considered a waste of time by most physicians, it is a Veterans Administration requirement in establishing initial service connection. However, most doctors will be examining and working on reports for veterans who have already had service connection established, and are conducting the examination to determine whether the condition has improved, regressed or remained stationary. In such cases, the statement on the physician's letterhead is sufficient. Notarization is not required in these cases.

Since claims may be made months, or, in some cases, years after the physician has examined or treated the veteran for a given condition, the doctor should state in the body of his report whether the information is from his office or clinic records, or from memory. Since Veterans Administration adjudication personnel have among their number physicians, or they can obtain the advice of Veterans Administration doctors, the reports should be in professional language with no attempt to simplify the terminology for lay interpretation. Interpretation of the validity of the doctor's data in relation to the veteran's claim will be made by medical personnel. Therefore the reports should be as complete and detailed as possible.

In the report, the date of first treatment and the length of time the veteran has been observed by the doctor should be included. Details of the pertinent history and physical examination are essential. The detailed medical findings, both physical and laboratory, should be included. For instance, degree of extension or flexion of an ankle may be very important in determining adjudication results. Such detailed medical findings should be listed by the reporting physician. When this is done, the final diagnosis made by the doctor can be interpreted in the light of the data that led to the making of the diagnosis. It is not sufficient merely to state that the veteran was treated for a given condition, without giving some of the pertinent facts relative to the condition in the particular veteran. If laboratory

V 1
194

tests or roentgenologic or other special examinations are done, reports of these should be included, if such reports are available. Some of these data may be valuable to aid the Veterans Administration in establishing the merit of a veteran's claim.

In summary, the medical report for the veteran for adjudication purposes should be complete and as detailed as possible. History, physical examination, laboratory and special examinations, with dates of period of observation and performance of examinations, are desired. Only with such complete reports can justice to the claim of the veteran be done by the Veterans Administration adjudication agencies.

T. O. KRAABEL,
Director, National Rehabilitation Commission, The American Legion, Washington, D. C.

Medical Motion Pictures

FILM REVIEWS

Indirect Inguinal Hernia. 16 mm., black and white, silent (2 reels). Prepared in 1929 and produced in collaboration with the American College of Surgeons and Daniel L. Borden, M.D., Washington, D. C. Procurable on rental or purchase from Encyclopaedia Britannica Films, Inc., 1150 Wilmette Avenue, Wilmette, Ill.

Reel I, **Surgical Anatomy,** 394 feet, showing time sixteen minutes.

By animation and dissection on a cadaver some of the factors involved in the production of an indirect inguinal hernia and the anatomy encountered in performing an indirect inguinal herniotomy are illustrated. The dissection is unusually good and the structures encountered are well pointed out and captioned.

Reel II, **Clinical Aspects,** 280 feet, showing time eleven minutes.

This reel deals with the diagnosis of an indirect inguinal hernia. By means of animation superimposed on a patient, the pathologic processes sometimes present in a hernia are well depicted. Complete, incomplete, reducible, nonreducible and strangulated hernias are all illustrated.

Although these motion pictures were produced some time ago, they are basic type films and can be recommended for use in teaching residents, interns and especially medical students. They would be very valuable as an adjunct to lectures on the subject of hernias as well as surgical anatomy and anatomy.

In both reels, the animation is simple and well done and the photography is clear. From a production point of view, these films are superior in some respects to many which have been produced in more recent years.

Curare in Barbiturate Oxygen Anesthesia. 16 mm., color, sound, 700 feet (1 reel), showing time nineteen minutes. Prepared by T. C. Davison, M.D., and A. H. Letton, M.D., Atlanta, Ga. Produced in 1948 and procurable on loan from E. R. Squibb & Sons, Motion Picture Department, 745 Fifth Avenue, New York 22.

This film presents mainly the way patients are handled at the Georgia Baptist Hospital and demonstrates that more relaxation can be secured and intravenous administration of less thiopental sodium required, if both thiopental and curare are administered. It illustrates a vagotomy with patient under thiopental-oxygen-intocostrin® anesthesia. Several other surgical procedures under the same anesthetic management are briefly shown. More emphasis is placed on the surgical and general hospital care of patients than on detailed information pertaining to the anesthetic management.

The statistical material presented by the narrator dealing with the advantages of thiopental-oxygen-curare mixtures over thiopental-oxygen alone would have been clearer and more concise if given in table form. Since these drugs do not have truly analgesic properties, and both thiopental and intocostrin® have potentially great and not always predictable depressant action as regards respiration, there should be a demonstration by the responsible physicians of the diagnosis and management of the physiologic changes produced by such drugs. More discussion of the treatment of overdosage is needed, as well as enumeration of, and means of avoiding, the various complications that may occur during or following either intravenous administration of thiopental or administration of curare.

In the introductory part of this motion picture, there is a considerable amount of unnecessary footage which shows in great detail a patient leaving her car walking up the steps to the entrance of the hospital, routine of admission and medical examination for a peptic ulcer followed by the surgical operation and her convalescence period. A greater part of this should have been deleted and the opening scene replaced by showing the operating room and patient ready for surgery.

The photography is excellent. However, from a production standpoint the film is very poorly done.

Thyroidectomy by Electro-Surgery. 16 mm., color, silent, 787 feet (2 reels), showing time thirty minutes. Prepared in 1941 by and procurable on loan from Arnold S. Jackson, M.D., Jackson Clinic, Madison, Wis.

This film is designed to show the preoperative procedure, the operative technic of a thyroidectomy and postoperative care at the Jackson Clinic. It demonstrates a skilful method of excising most of the thyroid gland by the use of the electrocautery. This method necessitates local anesthesia, which in turn demands heavier preoperative medication, longer incisions, wider exposure, less pulling on retractors and much more gentleness. The large vessels must be recognized and tied separately by ligature. Hemostasis must be completed by suturing the capsular edges of the remnant; to do this the remnant should be hollowed out to form a concave surface. All these technics are necessary to accompany the electrocautery method.

The second reel is more or less a repetition of the first reel. The diagnostic tests portrayed are of little value to one sufficiently informed to appreciate the technic.

The technic and surgical anatomy are not sufficiently detailed to be of much use to the uninitiated but are of value and interest to a surgeon already familiar with surgery of goiter.

The film was made before the advent of thiouracil derivatives. The short discussion on preoperative treatment, evaluation of risk and two stage operations is antiquated but because of its brevity does not detract from the film.

The photography of the patients is only fair; however, the surgical sequences are excellent.

Supradiaphragmatic Gastric Vagotomy for Peptic Ulcer, the Abdominal Approach. 16 mm., color, silent, 550 feet (2 reels), showing time twenty minutes. Prepared in 1948 by Lester R. Dragstedt, M.D., Ph.D., Chairman, Department of Surgery, University of Chicago. Procurable on loan from Davis & Geck, Inc., 57 Willoughby Street, Brooklyn 1.

Reel I: A series of drawings illustrates the technic of the operation and the anatomy of the vagus nerves at the lower end of the esophagus and at the upper part of the stomach.

Reel II presents an excellent demonstration of the technic of transabdominal vagotomy as performed by the author.

Although the operation is done on a patient who has a duodenal ulcer without obstruction, the ulcer is not demonstrated sufficiently well for one to note its size or position and whether it is causing obstruction. The operative procedure is illustrated by a series of drawings. An upper left rectus incision is made. The triangular ligament is divided enabling mesial retraction of the left lobe of the liver. The mediastinum is opened and traction is placed on the esophagus to bring it into the abdomen for a distance of about 5 cm. The vagus nerves are demonstrated and approximately 3 to 4 cm. excised. The cut ends are ligated. The incised visceral peritoneum is resutured and the mediastinum and abdominal wall closed.

The postoperative care of the patient's stomach by use of an indwelling gastric tube to which is attached a continuous suction apparatus is depicted briefly. Additional information on prevention of impending dehydration, toxemia and electrolyte imbalance, and marked loss of gastric secretion, which is sometimes prolonged for several days, would be of value.

Much footage was used in closing the incision, which seems to be a routine closure.

This motion picture is recommended for showing to general surgeons, general practitioners, residents, interns and medical students.

Photography, animation and visual demonstration are excellent with the exception of a few places in Reel II, where the surgeon's right hand obstructs the operative field. This part could well be eliminated.

Council on Medical Education and Hospitals

DISCONTINUATION OF GRANTING TEMPORARY APPROVAL TO RESIDENCY TRAINING PROGRAMS

The Council on Medical Education and Hospitals has voted not to grant any additional temporary approvals for residency training programs. This action, effective as of Jan. 1, 1949, was taken in concurrence with the Advisory Board for Medical Specialties. Hereafter, residency training programs will be considered for approval only after the programs have been inspected by representatives of the Council. The Council plans to inspect in the near future all residencies holding temporary approval as of Jan. 1, 1949. On the basis of the findings of the inspections, the Council in concurrence with the specialty boards concerned will decide whether to grant these residencies full approval or to discontinue approval.

DONALD G. ANDERSON, M.D., Secretary.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* Various Centers. June 20-22, Sept. 12-14. *Part II.* April 25-26. Exec. Sec., Mr. E. S. Elwood, 225 S. 15th St., Philadelphia 2.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY, INC. *Written.* Various Centers. July 15: Final date for filing application is April 15. *Oral.* April 10-14 and Oct. 16-20. Sec., Dr. Curtiss B. Hickcox, 745 Fifth Ave., New York 27.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: *Oral.* New York City, April 1-3. Sec., Dr. George M. Lewis, 66 East 66th Street, New York 21.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* New York City, March 23-25. Philadelphia, June 1-3. *Written.* Oct. 17. Final date for filing application is May 1. Asst. Sec.-Treas., Dr. W. A. Werrell, 1 Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* Chicago, June 1949. Sec., Dr. W. J. German, 310 Cedar Street, New Haven, Conn.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.: *Oral.* Chicago, May 8-14. Final date for filing application is April 1. Sec., Dr. Paul Titus, 1015 Highland Building, Pittsburgh 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* San Francisco, March 21-24; New York, June 11-15; St. Louis, Oct. 15-19; Boston Dec. Sec., Dr. S. J. Beach, 56 Ivie Rd., Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY. *Part I.* New York City, April 22-23; Atlanta, Ga., April 29-30; Indianapolis, May 6-7 and Denver, May 13-14. *Part II.* New York City, Jan. 1950. Final date for filing application for Part II is Aug. 15. Address: Dr. Francis M. McKeever, 1126 W. 6th St., Los Angeles 14, Calif.

AMERICAN BOARD OF OTOLARYNGOLOGY: New York, May 11-14, Chicago, Oct. 4-7. Sec., Dr. D. M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PATHOLOGY: Boston, April 12-13. Sec., Dr. Robert A. Moore, 507 S. Euclid Ave., St. Louis 10, Mo.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Baltimore, May 7-9. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Rd., Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE. Atlantic City, June 4-5. Sec., Dr. R. L. Bennett, 30 N. Michigan Blvd., Chicago.

AMERICAN BOARD OF PLASTIC SURGERY: Examinations are given in June and November of each year in the home town of applicants. Sec., Treas., Dr. Louis T. Byars, 400 Metropolitan Bldg., St. Louis, Mo.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC. December, New York City. Sec., Dr. F. J. Braceland, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY. Atlantic City, June 2-4. Sec., Dr. B. R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various Centers, October. Final date for filing application is July 1. Sec., Dr. J. Stewart Rodman, 225 S. 15th St., Philadelphia.

AMERICAN BOARD OF UROLOGY: Feb. 1950. Sec., Dr. Harry Culver, 7935 Sunnyside Road, Minneapolis 18, Minn.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 28-30. Sec., Dr. D. G. Gill, 519 Dexter Ave., Montgomery.

ARKANSAS: * Little Rock, June 9-10. Sec., Dr. L. J. Kosminsky, Texarkana. *Eclectic.* Little Rock, June 9-10. Sec., Dr. C. H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Examination.* San Francisco, June 20-23. Sec., Dr. Frederick N. Scatena, 1020 N St., Sacramento.

COLORADO: * *Endorsement,* Denver., April 5. *Written,* Denver, June 20-22. Sec., Dr. W. W. King, 831 Republic Bldg., Denver 2.

DELAWARE: Dover, July 12-14. Sec., Dr. J. S. McDaniel, 229 South State St., Dover.

DISTRICT OF COLUMBIA: * *Written,* Washington, May 9-10. Sec., Dr. George C. Ruhland, 4130 Municipal Bldg., Washington.

FLORIDA: * *Examination,* Jacksonville, June 26-28. Sec., Dr. Frank D. Gray, 12 N. Rosalind Ave., Orlando.

GEORGIA: *Examination.* June, Atlanta and Augusta. *Reciprocity.* Atlanta, June. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: *Endorsement.* Agana, Last Friday of each month. Sec., Capt. C. K. Youngkin, Dept. of Public Health, Guam. % F.P.O., San Francisco, Calif.

HAWAII: * *Examination.* Honolulu, July 11-14. Sec., Dr. S. E. Doolittle, 881 S. Hotel St., Honolulu.

IDAHO: Boise, July 11-13. Sec., Miss Estella S. Mulliner, Bureau of Occupational Licenses, 355 State House, Boise.

ILLINOIS: Chicago, April 12-14. Supt. of Registration, Mr. Fred W. Ruegg, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 21-23. Sec. Board of Medical Registration and Examination. Dr. Paul R. Tindall, 416 K. of P. Bldg., Indianapolis.

IOWA: * *Examination.* Iowa City, June 13-15. Sec., Dr. M. A. Royal, 506 Fleming Bldg., Des Moines.

KANSAS: Kansas City, June 1-2. Sec., J. F. Hassig, 905 North 7th St., Kansas City, Kans.

KENTUCKY: *Examination.* Louisville, June 15-17. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville 2.

MARYLAND: *Examination.* Baltimore, June 21-24. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore. *Homeopathic.* Baltimore, June 14-15. Sec., Dr. John A. Evans, 612 West 40th St., Baltimore.

MINNESOTA: * Minneapolis, April 19-21. Sec., Dr. J. F. Du Bois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: Jackson, June 21-22. Asst. Sec., Dr. R. N. Whitfield, State Board of Health, Jackson.

MISSOURI: *Examination.* St. Louis, May 30-31 and June 8-10. Exec. Sec., Mr. John A. Hailey, Box 4, Jefferson City.

MONTANA: Helena, April 4-6. Sec., Dr. O. G. Klein, First National Bank Building, Helena.

NEBRASKA: * *Examination.* Omaha, June. Dir., Bureau of Examining Boards, Mr. Oscar F. Humble, 1009 State Capitol Building, Lincoln 9.

NEVADA: Carson City, May 2. Sec., Dr. G. H. Ross, 112 N. Curry Street, Carson City.

NEW JERSEY: *Examination.* Trenton, June 21-24. Sec., Dr. E. H. Hallinger, 28 West State Street, Trenton 8.

NEW MEXICO: * Santa Fe, April 11-12. Sec., Dr. V. E. Berchtold, 141 Palace Ave., Santa Fe.

NEW YORK: Albany, Buffalo, New York and Syracue, June 28-July 1, Sec., Dr. Jacob L. Lochner, 23 South Pearl St., Albany.

NORTH CAROLINA: *Endorsement.* Pinehurst, May 9. *Examination.* Raleigh, June 23-25. Sec., Dr. Ivan Procter, 226 Hillsboro St., Raleigh.

OHIO: *Endorsement.* Columbus, April 5. *Written.* Columbus, June. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OREGON: * *Endorsement.* Portland, April 29-30. *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July. Acting Sec., Mrs. B. G. Steiner, 351 Education Bldg., Harrisburg.

RHODE ISLAND: * *Examination.* Providence, April 7-8. Chief, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 27-29. *Endorsement.* Columbia, March 31, April 4, May 2, June 27-28, Aug. 1, Sept. 5 and Oct. 3. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA: * *Examination.* Pierre, July 19. Sec., Dr. G. J. Van Heuvelen, Capitol Bldg., Pierre.

TENNESSEE: * *Examination.* Memphis, March 23-24. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis.

TEXAS: *Examination.* Austin, June 16-18. Sec., Dr. M. H. Crabb, 209 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July. Sec., Dept. of Registration. Miss Rena B. Loomis, 324 State Capitol Bldg., Salt Lake City.

VIRGINIA: *Examination.* Richmond, June 17-18. *Reciprocity.* Richmond, June 16. Dr. K. D. Graves, 631 First St., S.W., Roanoke.

WASHINGTON: * Seattle, July. Sec., Mr. Edward C. Dohm, Department of Licenses, Olympia.

WEST VIRGINIA: Charleston, April 7-9. Sec., Dr. N. H. Dyer, State Capitol, Charleston 5.

WISCONSIN: * *Examination.* Milwaukee, June 28-30. Sec., Dr. C. A. Dawson, Tremont Bldg., River Falls.

WYOMING: Cheyenne, June 6. Sec., Dr. Franklin D. Yoder, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARKANSAS: *Examination.* Little Rock, May 3. Sec., Mr. L. E. Gebauer, 1002 Donaghey Bldg., Little Rock.

COLORADO: *Examination.* Denver, June 1-2. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

DISTRICT OF COLUMBIA: *Examination.* Washington, April 18-19. Sec., Dr. George C. Ruhland, 4130 Municipal Bldg., Washington.

FLORIDA. *Examination.* Gainesville, June 11. Sec., Mr. M. W. Emmel, University of Florida, Gainesville.

IOWA: *Examination.* Des Moines, April 12. Sec., Dr. Ben H. Peterson, Coe College, Cedar Rapids.

MICHIGAN: *Examination.* Detroit and Ann Arbor, May 13-14. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing 15.

MINNESOTA: *Examination.* April 4, June and Oct. Sec.-Treas., Dr. Raymond N. Dieter, 105 Millard Hall, Univ. of Minnesota, Minneapolis.

NEW MEXICO: *Examination.* Santa Fe, March 20. Sec., Miss Marguerite Kilkenny, 110 W. Houghton St., Santa Fe.

OKLAHOMA: April 15. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

OREGON: Portland, June 18, Sept. 3 and Dec. 3. Sec., Mr. Charles D. Byrne, State Board of Higher Education, Eugene.

SOUTH DAKOTA: Vermillion, June 3-4. Dr. G. M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: Memphis, March 21-22 and July 8-9. Sec., Dr. O. W. Hyman, 874 Union Ave., Memphis 3.

WISCONSIN: Madison, April 2. Milwaukee, June 4. Sec., Prof. W. H. Barber, Ripon College, Ripon

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1938 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Public Health, New York

38:1361-1498 (Oct.) 1948. **Partial Index**

*Recent Developments in Treatment of Syphilis. E. W. Thomas.—p. 1361.
Some Unmet Needs in Tuberculosis Control—Challenge for the Future. W. P. Shepard.—p. 1370.
Physical Disability: National Problem. H. A. Rusk and E. J. Taylor.—p. 1381.
Participation of Puerto Rico in Federal Health and Hospital Program. E. G. Morales.—p. 1387.
Coordination of Preventive and Curative Services in Maryland. W. H. F. Warthen.—p. 1393.
Comparison of Immunogenic and Anaphylactogenic Properties of Rocky Mountain Spotted Fever Vaccines Prepared from Infected Yolk Sacs and from Infected Tick Tissue. D. Lackman and R. R. Parker.—1402.
Laboratory Procedure for Evaluating Practical Performance of Quaternary Ammonium and Other Germicides Proposed for Sanitizing Food Utensils. G. R. Weber and L. A. Black.—p. 1405.
Abortion as Cause of Death. C. Tietze.—p. 1434.
Epidemiologic Approach to Accident Prevention. E. Press.—p. 1442.

Treatment of Syphilis.—Thomas evaluated the present status of penicillin in the treatment of syphilis. The time-dose relationships of therapy with aqueous solutions of penicillin are different from those with slowly absorbed preparations. So far, the best results in the treatment of early syphilis seem to have been obtained with daily injections of 300,000 to 600,000 units of penicillin in oil and beeswax for fifteen days. Procaine penicillin G in oil and 2 per cent aluminum monostearate can now be substituted for penicillin in oil and beeswax, and individual injections of this preparation do not have to be given as frequently as with penicillin in oil and beeswax. Probably two injections of 600,000 units of this preparation a week for two or three weeks will accomplish as much as daily injections of 300,000 units of penicillin in oil and beeswax for fifteen days. Neurosyphilis should be treated with at least 6,000,000 units of penicillin over a period of not less than fifteen days and preferably three weeks. Injections of 600,000 units of procaine penicillin in oil and aluminum monostearate three times a week for three weeks should prove sufficient therapy for most cases of neurosyphilis. For late symptomatic and late latent syphilis from 4,000,000 to 6,000,000 units of penicillin should be given over a period of not less than fifteen days. In most cases of late syphilis, whether symptomatic or asymptomatic, it is impossible to reverse positive serologic reactions for syphilis to negative within five or more years. Such patients should be observed with quantitative serologic tests at regular intervals. Great rises in quantitative tests from previous levels, sustained for several weeks or months, are an indication for further therapy.

American Practitioner, Philadelphia

3:131-196 (Nov.) 1948

Headache: Review of Literature. A. P. Friedman.—p. 131.
Management of Diabetes Mellitus. G. G. Duncan.—p. 139.
How Frequently Is Nervousness the Cause of Difficulty in Swallowing? P. P. Vinson.—p. 152.
Gout. W. K. Myers.—p. 158.
Causes of Hematuria. S. S. Baird.—p. 162.
Pathologic Physiology of Hemoglobin Formation. C. A. Finch.—p. 165.
Psychosomatic Problems of the Aged. L. C. Sanders.—p. 169.
Ventricular Aneurysm: Report of 2 Cases. W. T. Zimdahl and S. Busuego.—p. 185.
Jaundice. P. Thorek.—p. 192.

Journal of Bone and Joint Surgery, Boston

30-A:805-1062 (Oct.) 1948. **Partial Index**

Bone Lesions in Eosinophilic Granuloma, Hand-Schüller-Christian Disease, and Letterer-Siwe Disease. I. Ponseti.—p. 811.
Response of Quadriceps Femoris to Progressive-Resistance Exercises in Poliomyelitic Patients. T. L. Delorme, R. S. Schwab and A. L. Watkins.—p. 834.
Reconstruction of Metacarpophalangeal Joint with Metatarsal Transplant. W. C. Graham and D. C. Riordan.—p. 848.
Transplantation of Tibia and Fibula to Replace Femur Following Resection: "Turn-Up-Plasty" of Leg. C. P. Van Nes.—p. 854.
Transverse Rotation of Segments of Lower Extremity in Locomotion. A. S. Levens, V. T. Inman and J. A. Blosser.—p. 859.
Complete Dislocation of Talus. W. J. Newcomb and E. A. Brav.—p. 872.
*Occurrence and Management of Reflex Sympathetic Dystrophy (Causalgia of Extremities). J. W. Toumey.—p. 883.
Tenosynovitis of Extensor Carpi Ulnaris Tendon Sheath. D. D. Dickson and C. A. Luckey.—p. 903.
Synovectomy of Knee Joint: Review of Literature and Presentation of Cases. M. L. Pardee.—p. 908.
*Estrogens and Bone Formation in Human Female. Mary S. Sherman.—p 915.
*Streptomycin in Treatment of Chronic Infections of Bone. J. C. Wilson Jr.—p. 931.
Diffuse Inflammation of Cartilage: Case Report of Hitherto Unreported Entity. E. J. Gordon, A. W. Perlman and N. Schechter.—p. 944.
Accessory Tarsal Scaphoid. I. Zadek and A. M. Gold.—p. 957.
Vascular Complication of Disk Surgery. E. C. Holscher.—p. 968.
Criteria for Spine Fusion Following Removal of Protruded Nucleus Pulposus. G. A. Caldwell and W. B. Sheppard.—p. 971.
Rapid Method of Correcting Deformity in Scoliosis Preliminary to Fusion. V. A. Scudese.—p. 980.
Bone Disturbances in Injuries to Spinal Cord and Cauda Equina (Paraplegia): Their Prevention by Ambulation. A. S. Abramson.—p. 982.
Device in Which Springs Replace Action of Paralyzed Muscles of Arm. G. E. Ward, H. R. Bohlman and R. V. Wood.—p. 987.
Control of Forearm Rotation by Kirschner Wire. S. Bunnell and L. D. Howard Jr.—p. 992.
Operation for Old Dislocation of Shoulder. J. S. Neviaser.—p. 997.
Congenital Bilateral Complete Absence of Radius in Identical Twins. R. R. Goldenberg.—p. 1001.
Bilateral Fracture of Pars Interarticularis of Lumbar Neural Arch. M. B. Roche.—p. 1005.

Reflex Sympathetic Dystrophy (Causalgia of Extremities).—Toumey defines reflex sympathetic dystrophy as a disturbance of the sympathetic nervous system, characterized by pain and sympathetic phenomena which may follow traumas. There has been an enormous confusion of terms; the following terms were used in describing the 31 cases reviewed here: "reflex sympathetic dystrophy," "causalgia," "minor causalgia," "post-traumatic pain," "traumatic sciatica," "post-traumatic sympathetic phenomena," "Sudeck's atrophy" and "nerve injury." The diagnosis of reflex sympathetic dystrophy rests on the clinical picture of sympathetic phenomena, which include: coldness, changes in skin color, increased sweating, swelling and atrophy of skin and bone, plus the relief of pain, sweating and coldness by procaine sympathetic blocks. Sympathectomy is justified if good, but not permanent, results are obtained by the procaine sympathetic blocks. Sympathectomy was performed at the Lahey Clinic in the cases reviewed in this paper. It relieved pain in two thirds of the 31 cases. Surgery, such as arthrodeses of painful joints, may be required in addition to sympathectomy. The best results were achieved in patients who had had reflex sympathetic dystrophy for relatively short periods and in those who were in the younger age groups. If the result of the block is poor, the result of the sympathectomy will also be poor, but even though the result of the block is good, the result of sympathectomy will not be good in all cases. The prevention of reflex sympathetic dystrophy depends on treating traumas so that pain is minimized and function is restored to the extremity as rapidly as possible.

Estrogens and Bone Formation.—Sherman shows that in the human female estrogens are in some fashion concerned with the rate of growth and maturation of the skeleton. Investigators have studied postmenopausal osteoporosis as a hormonal deficiency and have found that they could produce and maintain calcium retention in the human being by the injection of estrogens. However, these workers admit that irrefutable evidence that the bones have actually become more dense has never been obtained by them. The author presents the history of a patient in whom this was possible. The patient, a woman, aged 58, had had a surgical menopause

seventeen years before, but the diagnosis of postmenopausal osteoporosis could not explain the greatly elevated phosphatase level or the roentgenographic appearance of the skull. Moreover, it is hard to conceive of a generalized process which would spare one tibia while the other practically disappeared, without involvement of the fibula, and affect the lumbar spine and pelvis so severely, while the rest of the trunk remained relatively normal. It was concluded that the picture could best be interpreted as a severe postmenopausal osteoporosis, superimposed on previously existing Paget's disease. Massive estrogen therapy was followed by a remission of clinical symptoms and by actual reconstitution of bone. Withdrawal of the estrogen produced an exacerbation; its readministration was again followed by improvement. For over two years the patient has been kept on daily doses of 2,000 to 10,000 rat units (0.33 to 1.66 mg.) of estradiol benzoate; during this time she has maintained her improvement and has not shown untoward symptoms.

Streptomycin in Chronic Infections of Bone.—The purpose of the study conducted by Wilson was to determine whether or not the systemic and local use of streptomycin, in addition to thorough sequestrectomy and painstaking care of the wound, would hasten the healing of wounds in patients ill with osteomyelitis of long duration. Twenty-five cases of chronic osteomyelitis are reported in which discharging sinuses had been present for an average of nineteen months. Many types of treatment had been tried, without success. A plan of therapy was evolved on the following principles: (1) thorough investigation of the wound bacteria; (2) radical sequestrectomy after adequate preoperative preparation; (3) the use of streptomycin and penicillin before, during and after surgery; (4) painstaking care of the wound after surgery to prevent contamination. Twenty-one patients have responded favorably, but 4 patients failed to respond and have had amputation. The author emphasizes that the use of streptomycin offers no panacea for the treatment of chronic osteomyelitis. The drug cannot replace adequate surgery, but, when combined with thorough sequestrectomy, it is beneficial.

New York State Journal of Medicine, New York

48:2207-2318 (Oct. 15) 1948

Diagnosis and Management of Postcholecystectomy Syndrome. J. R. Twiss and R. F. Carter.—p. 2245.
Acute Pancreatitis. H. L. Bockus and E. C. Raffensperger.—p. 2252.
Streptomycin in Tuberculosis: Experimental Observations on Efficacy, Shortcomings, and Limitations. W. H. Feldman.—p. 2260.
*Rickettsialpox. H. M. Rose.—p. 2266.
Evaluation of Present Status of Antihistaminic Substances. W. C. Spain and F. A. Pflum.—p. 2272.
Guided Liver Biopsy Through Laparotomy Incision. E. E. Jemerin.—p. 2276.
Selection of Hypertensive Patients for Sympathectomy. H. I. Russek, J. L. Southworth and B. L. Zohman.—p. 2278.

Rickettsialpox.—According to Rose rickettsialpox is a disease entity which was first recognized in 1946 and has not been observed outside New York city. Huebner and others identified the causative agent as Rickettsia akari and showed that the infection is, in all likelihood, transmitted to man by the bite of a rodent mite, Allodermanyssus sanguineus. These investigators isolated R. akari from mice trapped in apartment houses when cases of rickettsialpox had occurred. Rickettsialpox is now common in New York city. More than 350 cases have been reported to the department of health since the spring of 1946. The author reports 3 cases which illustrate important features of the disease and reviews observations on 17 patients who were hospitalized for rickettsialpox. In 15 of the 17 patients a primary lesion could be identified with certainty. These consisted of areas of erythema and induration from 1.0 to 2.5 cm. in diameter. The rash usually appeared within six days after the onset of fever. The constitutional symptoms were fever, headache, chills and backache or general muscular aching. These symptoms appeared from two to seven days after the appearance of the primary lesion. The fever curve was of the remittent type and fell to normal by lysis, generally within a week. Headache was a prominent feature and was usually frontal. Attempts were made in 9 patients to recover the causative agent by inoculating blood collected early in the disease into mice, guinea pigs and chick embryos. R. akari was successfully isolated from 7 of the patients by mouse inoculation, and from 1 of these patients the organism was also cultivated directly in chick embryos. Rickettsialpox is a nonfatal disease and only symptomatic measures are required. A laboratory infection with rickettsialpox was not modified by streptomycin.

Obstetrical & Gynecological Survey, Baltimore

3:603-778 (Oct.) 1948

Some Functional Activities of Placental Trophoblast. G. B. Wislocki, E. W. Dempsey and D. W. Fawcett.—p. 604.
Placental Dysfunction in Eclamptogenic Toxemias. E. W. Page.—p. 615.
Patterns of Uterine Contractility in Women During Pregnancy. S. R. M. Reynolds, L. M. Hellman and P. Bruns.—p. 629.
Pregnancy and The Thyroid Gland. J. P. Peters, Evelyn B. Man and M. Heinemann.—p. 647.
Excretion of Various Hormone Metabolites in Normal Pregnancy. E. H. Venning.—p. 661.
Urinary Excretion of Ketosteroids in Pregnancy. K. Dobriner, S. Lieberman and C. P. Rhoads.—p. 677.
Endocrine Patterns in Abortion. Eleanor Delfs and G. E. S. Jones.—p. 680.
Experimental Studies on Nutrition in Pregnancy. J. Warkany.—p. 693.
Biochemical Assessment of Nutritional Status During Pregnancy. W. J. Darby, R. O. Cannon and Margaret M. Kaser.—p. 704.
Nutritional Needs in Pregnancy in Relation to Nutritional Intakes as Shown by Dietary Histories. Bertha S. Burke.—p. 716.
*Diet Studies in Pregnant Patients. W. J. Dieckmann, D. F. Turner, E. J. Meiller, M. T. Straube and others.—p. 731.
Hemorrhagic Tendencies in Toxemia of Pregnancy (Practical Evaluation and Management). F. S. Kellogg.—p. 746.
Some Observations on Liver Function in Pregnancy. E. W. Munnell.—p. 758.
Clinical Management of Late Toxemias of Pregnancy. S. A. Cosgrove and L. C. Chesley.—p. 769.

Diet Studies in Pregnancies.—Dieckmann and his associates show that reports of the value of an adequate amount of the proper foods in pregnancy show major inconsistencies. In a preliminary study of 100 patients the protein intake of most of the women was found to be below 85 Gm. per day. In some cases, instruction to increase the protein intake resulted in only small changes in food intake. In other cases, improvements were made. A preliminary study of the data demonstrates the value of weighing the food intake and periodically determining the protein balance. Studies on nutrition in pregnancy are being carried out in several other institutions. It is hoped that the results can be pooled and definite conclusions, based on an adequate number of patients, can be made as to what foods the pregnant woman should eat.

Proc. of Staff Meet. of Mayo Clinic, Rochester, Minn.

23:481-520 (Oct. 27) 1948

*Cardiac Catheterization in Diagnosis of Various Cardiac Malformations and Diseases. H. B. Burchell, R. L. Parker, T. J. Dry and others.—p. 481.
Characteristics of Resistance-Wire Manometer for Measuring Blood Pressure in Cardiac Catheterization Studies. E. H. Lambert and R. E. Jones.—p. 487.
General and Special Technics in Cardiac Catheterization. E. H. Wood, J. E. Geraci, A. A. Pollack and others.—p. 494.
Interatrial Mixing of Blood and Pulmonary Circulatory Dynamics in Atrial Septal Defects. B. E. Taylor, J. E. Geraci, A. A. Pollack and others.—p. 500.
Patent Ductus Arteriosus with Pulmonary Hypertension and Atypical Clinical Findings. J. W. DuShane and G. E. Montgomery Jr.—p. 505.
Ventricular Septal Defect and Pulmonary Hypertension Without Hypoxemia. H. B. Burchell, B. E. Taylor, A. A. Pollack and others.—p. 507.
Atrial Septal Defect and Probable Tricuspid Atresia in Adults. J. E. Geraci, T. J. Dry and H. B. Burchell.—p. 510.
Pulmonary Stenosis Without Septal Defect. A. A. Pollack, B. E. Taylor, H. M. Odel and H. B. Burchell.—p. 516.

Cardiac Catheterization.—This report by Burchell and his associates is based on 60 cardiac catheterizations on patients who presented problems in diagnosis. The method provides information as to (1) the parts of the heart, intrathoracic veins or great vessels that may be entered by the catheter and recognized roentgenoscopically, (2) the oxygen content of the blood from the parts catheterized and (3) the pressure in the chambers or vessels that have been catheterized. A fourth feature, the recording of intraventricular electrocardiograms, will eventually be incorporated into the routine catheterization procedure. Complete failure of the catheter to enter the thoracic cavity occurred once. In this patient the superior

vena cava was apparently anomalous or obstructed. Partial failure, such as inability to get into the pulmonary artery, even when pulmonary stenosis was considered not to be present, or the inferior vena cava or the right ventricle, has been experienced in as high as 25 per cent of the patients with congenital cardiac lesions. The authors have found cardiac catheterization in congenital cardiac disease particularly helpful in (1) the differentiation of Eisenmenger's complex from pulmonary stenosis (tetralogy of Fallot), (2) the recognition of atrial and ventricular septal defects when the diagnosis was in doubt clinically, (3) the investigation for a patent ductus arteriosus when a typical murmur was absent and (4) the diagnosis of essential pulmonary hypertension. In patients with tetralogy of Fallot, the authors regard catheterization only occasionally indicated for diagnosis, because of expected difficulties in catheterization and because they have considerable confidence in the oximetric test during exercise. Catheterization is of value in any condition that may simulate congenital heart disease, such as essential pulmonary hypertension. It has a wide field of usefulness as a method to be utilized for clinical investigation, particularly when information on cardiac output in a steady physiologic state is wished.

Texas State Journal of Medicine, Fort Worth

44:413-484 (Oct.) 1948

Anesthesia Study Commissions. R. J. Whitacre.—p. 419.
Anesthetic Problems of a Doctor Doing General Practice. J. Pryor. —p. 422.
Scope of Plastic Surgery. T. G. Blocker.—p. 427.
Free Full-Thickness Buried Skin Grafts in Repair of Hernias. R. A. Richeson —p. 430.
Fascia-Lata Transplant in Regression of Retrotarsal Fat in Ophthalmosteresis. W. O. Murphy.—p. 435.
Nasal and Postoperative Tonsil and Adenoid Hemorrhage: Prevention and Control. C. E. Ball.—p. 437.
Treatment of Fractures in General Practice. L. C. Powell.—p. 440.
Diagnosis and Treatment of Protruded Lumbar Intervertebral Disks. C. D. Wilson.—p. 445.
Congenital Evisceration with Atresia of Colon. R. G. Lemon and J. N. Walker.—p. 449.
Congenital Fibrous Bands at Anorectal Line: Possible Etiologic Factor in Colic and Constipation. J. M. Coleman.—p. 454.
Salpingiosis (Endosalpingiosis): Case Report. Evelyn Gass Powers and O. N. Hooker.—p. 457.
Reevaluation of Low Cervical Cesarean Section. R. P. McDonald. —p. 460.
Foreign Body Reaction to Sutures and Other Materials. S. A. Wallace and K. L. Brown.—p. 463.
Translocation of Body Fluids in Chronic Disease. E. B. Hay.—p. 467.

West Virginia Medical Journal, Charleston

44:265-292 (Oct.) 1948

Pharmacology of Antihistaminic Agents. D. F. Marsh.—p. 265.
Hypertension Today (Part II—The Rice Diet). M. Koenigsberg. —p. 269.
Medical Potpourri. L. R. Lambert.—p. 279.
Some Practical Considerations in Use of Chemotherapy and Antibiotics in Treatment of Upper Respiratory Infection. H. M. Goodyear. —p. 284.

44:293-324 (Nov.) 1948

Surgery in Infancy and Early Childhood. B. Bradford Jr.—p. 293.
*Diagnosis of Acute Poliomyelitis. M. B. Kehoe.—p. 299.
Hypertension Today (Part III—Low (200 mg.) Sodium Diet). M. Koenigsberg.—p. 302.
Dermatoses of Allergic Etiology. J. W. Thomas.—p. 308.

Diagnosis of Acute Poliomyelitis.—Kehoe shows that poliomyelitis may present difficulties in diagnosis. Among 100 patients admitted to a hospital for crippled children with a presumptive diagnosis of poliomyelitis, the diagnosis was established in 77, whereas the other 23 were subsequently proved to have other diseases. There is no single pathognomonic element of history, symptom, sign, physical or laboratory observations which will offer a positive diagnosis of acute anterior poliomyelitis. Accurate history, a thorough physical examination and good clinical judgment must all be combined to make the diagnosis. However, cervical rigidity, muscular weakness or paralysis, muscular soreness and loss of deep tendon reflexes in the involved areas are among the most significant findings which must be sought, together with the lesser pathognomonic findings of moderate temperature elevation, headache, irritability, nausea, vomiting and constipation. A series of symptoms found in many acute diseases but rarely in poliomyelitis is listed.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

British Journal of Radiology, London

21:481-530 (Oct.) 1948

*Observations upon Lymphopenia of X-Ray Irradiation. C. H. G. Price. —p. 481.
Surface and Emergent Doses in Radiotherapy. J. R. Clarkson and R. J. T. Herbert.—p. 494.
Radiotherapy in Dermatologic Conditions. R. T. Brain.—p. 501.
Penetrating Ulcer of Descending Duodenum with Severe Secondary Anemia Caused by Foreign Body. A. Elkeles.—p. 508.
Note on Apparatus for Angiocardiography. T. H. Hills.—p. 511.
Observations on Certain Congenital Abnormalities of Hand in African Natives. J. H. Smitham.—p. 513.
Gastric Varices. E. Samuel.—p. 519.
Appendix Situated Within Thorax. R. Fawcitt.—p. 523.
Appendiceal Calculus. G. R. Airth.—p. 526.

Lymphopenia of Roentgen Irradiation.—Price presents an analysis of the hematologic data collected during the treatment of a group of 16 women with 200 kilovolt roentgen rays. The observed response of the lymphocytes was characteristic in type and can be correlated with the integral dose. The major change in the total lymphocyte count takes place during the early part of a course of treatment. It may be the result of the direct action of the radiation, and the drop in the total lymphocyte count due to this is large and relatively rapid. The further drop in the total lymphocyte count which takes place in addition to this may be due to the indirect action of the radiation, which effect tends to diminish as the dose of radiation increases. Eventually, a stage is reached at which further irradiation, at the rates of dosage here considered, causes only a very small change in the total lymphocyte count.

Edinburgh Medical Journal

55:449-512 (Aug.) 1948

Arterial Embolism. J. R. Learmonth.—p. 449.
Comparison of Maternity Hospital Records During Last Twenty Years as Basis for Thoughts for Future Improvement of Midwifery. W. F. T. Haultain.—p. 463.
Infantile Cerebral Hemiplegia—Clinical Features and Pathologic Anatomy. R. M. Stewart.—p. 488.

Transactions Royal Soc. Trop. Med. and Hyg., London

42:105-206 (Sept.) 1948. **Partial Index**

*Pulmonary Schistosomiasis. M. Erfan.—p. 109.
Observations on Development of Resistance to Vivax Malaria. C. R. B. Blackburn.—p. 117.
Treatment of Epidemic Typhus with Chloromycetin. E. H. Payne, E. A. Sharp and J. A. Knaudt.—p. 163.
Mite Typhus Fever in Assam and Burma, 1944-1946. P. H. A. Willcox. —p. 171.
Fatal Case of Generalized Amebiasis Due to Protozoon Closely Resembling, if not Identical with, Iodamoeba Bütschlii. E. H. Derrick and C. M. Wenyon.—p. 191.

Pulmonary Schistosomiasis.—According to Erfan pulmonary schistosomiasis occurs in the early stage of schistosomal infection, during the passage of cercaria through the lungs and in the late stage from the deposition of ova and worms. The author describes the form due to the deposition of schistosome ova and worms in the lungs. In Egypt, 60 to 70 per cent of the inhabitants are infected with schistosomiasis which is pulmonary in at least 33 per cent of these. The disease affects males more often than females and is most common in children and young adults, the highest age incidence being between 10 and 30 years. It is a disease of agricultural workers. Two forms of pulmonary schistosomiasis can be recognized, bronchopulmonary and cardiovascular. In the bronchopulmonary form the pathologic lesions are in the bronchioles and alveoli. Clinically, these manifest themselves in the form of bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary emphysema and pulmonary fibrosis. In the cardiovascular form the pathologic lesions are primarily in the pulmonary arterioles and, secondarily, in the pulmonary artery and its branches and in the right ventricle. The clinical picture of this form is similar to that of primary pulmonary endarteritis or Ayerza's disease. However, cyanosis, which is the most striking feature of Ayerza's disease, is absent in pulmonary schistosomiasis, and appears only when the right ventricle has failed. Early treatment with antimony compounds is important. In cases of

advanced disease with enlargement of the right ventricle, they must be used with caution, as they are toxic to the myocardium. They are definitely contraindicated when the right ventricle has failed. Heart failure is treated on ordinary lines with digitalis, venesection and mercurials.

Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

92:2957-3048 (Sept. 25) 1948. **Partial Index**

*Treatment of Ventricular and Duodenal Ulcers with Succus Liquiritiae. F. E. Revers.—p. 2968.
Results of Streptomycin Treatment in 19 Patients with Influenzal Meningitis: Comparison with Earlier Results. W. J. Bruins Slot, L. A. Hulst and H. W. Stenvers.—p. 2973.
Urea Culture Medium as Aid in the Routine Examination of Feces and Urine for Typhoid, Paratyphoid and Dysentery Bacteria. J. A. de Nooy.—p. 2989.
Determination of Prothrombin Time During Treatment with Dicumarol. T. Strengers and H. H. Lindeboom.

Treatment of Gastric Ulcer with Licorice Extract.—Revers says that two years ago he first reported on the administration of succus liquiritiae (licorice extract or glycyrrhiza extract) to patients with gastric and duodenal ulcers. A paste-like consistency of the extract is obtained by mixing 100 Gm. of glycyrrhiza extract in powder form with 50 Gm. of water. The patient with ulcer takes a teaspoonful of this paste three times a day. On the assumption that it exerts an influence on the wall of the stomach, the paste is given when the stomach is empty, that is, in the morning about an hour before breakfast, about half past 11 o'clock in the morning and in the evening before going to bed. In 27 of 48 patients treated in this manner the symptoms subsided between the first and fourth days; in 10 others between the fourth and eighth days, and in 6 others somewhat later. In 5 of the 48 patients the treatment remained ineffective. Favorable results were obtained with the glycyrrhiza extract also in patients with gastritis. Edema of the face and of the extremities developed in some of the patients during treatment, and these patients often complained of severe headaches, pressure in the chest and abdominal pains. Pharmacologic studies have demonstrated the presence of a spasmolytic substance in the drug.

Presse Médicale, Paris

56:753-768 (Oct. 30) 1948

*Glycemia in Diabetic Coma. R. Boulin.—p. 753.
Continued Prolonged Treatment of Amebiasis. Coumel, Molinier and Pedoya.—p. 754.
*Cyclic Desquamation of Epithelium of Urinary Passage in Relationship with Menstrual Cycle. L. L. Wasserman.—p. 755.

Glycemia in Diabetic Coma.—Boulin determined the glycemia in 81 patients with diabetic coma. At the onset of the coma the sugar in the blood varied from 1.11 to 12.20 Gm., and its average was 4.59 Gm. In 2 patients the amount varied from 1.20 to 2 Gm., and in 2 additional patients it varied from 1 Gm. to 1.20 Gm. and was therefore practically normal. These latter cases of diabetic coma in the absence of hyperglycemia justify the intravenous administration of isotonic dextrose solution. This technic does not present any inconvenience with regard to diuresis. Amounts up to 596 Gm. of isotonic dextrose solution have been administered intravenously without untoward reaction. The blood sugar tends to increase in proportion to the tendency of the alkaline reserve to decrease. The amount of insulin required does not correspond to the blood sugar level at the onset of the coma. Considerable amounts of the drug may be administered safely during the first six hours after the initiation of the treatment because hypoglycemia does not occur during this period, but from then on hypoglycemia may be latent and may be manifested up to the seventy-second hour when the patient has practically recovered and no longer receives insulin except for small doses at long intervals. The blood sugar level should be determined every three hours during the period of treatment with insulin.

Desquamation of Epithelium of Urinary Passage.—Wasserman observed on examination of the urinary sediment in 30,000 cases that there is no relationship between the intensity of the desquamation of the epithelium of the urinary tract and the course of or recovery from an inflammatory process localized in the pelvis of the kidney, ureters or urinary bladder. There is little desquamation of the epithelium of the urinary tract in men. This desquamation varies considerably in women because of its relationship with the cyclic activity of the ovaries. There was little desquamation in a group of 11 girls between the ages of 1 to 7 years. In a second group of 28 girls between the ages of 9 and 15 years there was little desquamation in those who did not menstruate. Menstruation was preceded by considerable desquamation, which was restored to normal the moment that menstruation started. The menstruation was preceded likewise by a period of considerable desquamation for four to eight days in a group of 20 young women between the ages of 16 and 23 years; desquamation was restored to normal with the onset of menstruation. In a group of 10 women between the ages of 57 and 76 years the slight desquamation observed was similar to that in the girls between the ages of 1 and 7 years. In women desquamation of the epithelium of the urinary tract is diminished before the beginning of the secretory activity of the ovary and is diminished after the establishment of the menopause.

Rivista dell'Istituto Sieroterapico Italiano, Rome

23:73-128 (April-June) 1948. **Partial Index**

*Fuchsin in Therapy of Cholera. A. Castellani.—p. 73.

Fuchsin in Therapy of Cholera.—Castellani found that basic fuchsin kills Vibrio comma organisms without desintegrating them. It is well tolerated by men and animals and it retains its bactericidal and bacteriostatic power on V. comma even when dissolved in liquids containing pepsin and other enzymes or proteins. Basic fuchsin, in doses of 0.10 Gm. with intervals of ten minutes, up to a daily dose which varies between 1 and 2 Gm., if administered after appearance of diarrhea in cholera and preferably before appearance of vomiting, will control an attack of cholera. Basic fuchsin can be given orally in capsules or pills. The author reports a cure of all patients who had this treatment.

Schweizerische medizinische Wochenschrift, Basel

78:1049-1076 (Oct. 30) 1948. **Partial Index**

Surgical Treatment of Congenital Cardiac Defect, Particularly of Morbus Caeruleus. M. Grob.—p. 1049.
Angiocardiography in Congenital Cardiac Defects. E. Rossi and A. Prader.—p. 1054.
Queenslandfever-Endemia in Bremgarten (Canton Aargau). V. Gutscher and K. Nufer.—p. 1064.
*Substances Preventing Coagulation of Blood. Contribution to Problem of Thrombosis. Z. Horn and L. Borsodi.—p. 1069.

Substances Preventing Coagulation of Blood.—Experiments carried out by Horn and Borsodi with fresh oxalated plasma of normal persons demonstrated that the thrombokinase is capable of inactivating the heparin and occasionally the antithrombin. But only one part of the total heparin may be adsorbed or become closely attached chemically, while the other part may still be circulating in the blood in a form that may be disposed of. Additional experiments showed that toluidine blue prevents the conversion of prothrombin into thrombin. Experiments with the plasma of 11 patients with thrombosis demonstrated that in the plasma of 9 of these patients the time of the separation of the fibrin by the action of the thrombin was not shortened by the thrombokinase or by the toluidine blue, suggesting that the heparin in the form that can be disposed of may be missing in the blood of patients with thrombosis. The absence of this part of the heparin in the blood does not present the only cause of thrombosis, but it may be considered as one of the predisposing factors. Another one is the reduction of the antithrombin content of the blood, which results in a reduced capacity of the serum to dissimilate the thrombin. This capacity depends not only on the antithrombin content but also on the presence in the serum of an activating factor of enzymatic character. It is likely that the latter factor compensates for the effect of the substance which converts the thrombin. It is suggested that for the causation of thrombosis there may be necessary the concurrence of the predisposing and of other factors such as the lability of the vegetative system and the effect of temperature on the coagulation.

V 1
194

Book Notices

Deafness, Tinnitus, and Vertigo. By Samuel J. Kopetzky, M.D., F.A.C.S., Director of Department and Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, New York. Cloth. Price, $7.50. Pp. 314, with 31 illustrations. Thomas Nelson & Sons, 385 Madison Ave., New York 17, 1948.

Any work by this distinguished otologist deserves the attention of all who are interested in the field of deafness and related subjects.

There is much which is factual in this book and a great deal which is theoretic. Thus the chapters on anatomy and physiology are not of a controversial nature and can be read with benefit to all. The essence of the author's theme is that in most cases of deafness, tinnitus and vertigo there is altered chemical composition of the blood due to a dysfunction of the enzymatic interplay. This is not presented as an entity justifying itself but as a key to purposeful therapy.

According to the author there are three types of deafness; congenital, nonprogressive and progressive deafness. He is primarily concerned with the latter type, and as regards progression of deafness makes this statement: "The prime agent in the production of the phenomenon of progressive loss of hearing is the same in all types of cases, the pertinent factor being dysfunction of the conduction and the acoustic perception mechanisms."

Biochemical studies of the blood in these latter cases show, in most, hypercalcemia and hypocalcemia, hypercholesteremia and vitamin B deficiencies. In many of the patients whose histories give evidence of vestibular disturbances there is also evidence of hypoproteinemia or hypoalbuminemia. Finally, approximately one quarter of the cases present, among other abnormalities in the chemistry of the blood, degrees of hypoglycemia.

Depending on the observations in the general physical examination, the examination of the ears and adjacent structures and the biochemistry of the blood, therapy is then predicated on specific indications. It comprises surgery when it will remove existing pathologic impedimenta to sound wave transmission to the end organ. The reader will be surprised to see that the freeing of intratympanic adhesions is more favorably considered than the fenestration operation, which receives remarkably short shrift. Jacobson's solution, histamine desensitization, diathermy and pneumomassage are recommended in selected cases, as is the currently prevalent radium therapy to the nasopharynx, and the unprevalent operation of incising the tendon of the tensor tympani muscle. When the local pathologic change is the result of systemic disease or dysfunction of the neuroglandular or endocrine system medical therapy will be required. Thus, depending on blood chemical findings, diets may be employed as in cases with an excess of urea nitrogen or uric acid, or when there is hypoglycemia. Vitamins are abundantly used, principally A for its relationship to urea clearance and hypercholesteremia and B for its effect on carbohydrate metabolism. In addition, amino acids, minerals and hormones, principally thyroid, estrogens and testosterone, are often used.

No practicing otologist could do else but joyfully welcome a physiologically based and practically successful method of therapy of these distressing conditions, for which actually little has heretofore been offered. If the author's findings are corroborated by other clinics and investigators, this may be an epochal work. But the method of approach as here presented is so new and factual laboratory findings so interwoven with theoretic considerations, that most careful workers will wish more factual evidence of the efficacy of this purposeful therapy. For the great and glaring weakness of the book is that there is no proof that this detailed biochemical humoral medical therapeutic approach actually accomplishes anything, though the author states that of 167 treated patients approximately 85 per cent had improved hearing acuity and reported lessened tinnitus. There is in this entire book but one audiogram purporting to show improved hearing after almost a year of the author's type of therapy, and this one audiogram is itself open to critical doubt as to whether the gain shown is significant or meaningful.

On Hospitals. By S. S. Goldwater, M.D. [Collected Works.] Cloth. Price, $9. Pp. 395, with 34 illustrations. Macmillan Co., 60 Fifth Ave., New York 11, 1947.

This book is a collection of selected material from the many writings of the late Dr. S. S. Goldwater, whose accomplishments in the field of hospital administration and hospital planning gained worldwide recognition. For the convenience of the reader, the material has been arranged in five main sections, each representing a group of closely related subjects. The first section is concerned with hospital administration and organization and deals primarily with the function and duties of the hospital administrator. The organization of the medical staff is the main topic of the second section, which also describes the mutual responsibilities and interrelationships of the hospital and the staff physicians. In the third section the relationship of the hospital to the community as a whole is clearly interpreted. This concerns also the functions of the controlling board and the opportunities and responsibilities that come to those who are privileged to serve as hospital trustees. The principles of hospital planning are described in the fourth section, while in the fifth are detailed descriptions and outlines of representative hospital plans.

The book is a valuable addition to the literature of the hospital field and will serve as a convenient and authoritative reference for hospital administrators and consultants, students of hospital administration and other personnel interested in the planning, organization and maintenance of hospital service.

The Salicylates: A Critical Bibliographic Review. By Martin Gross, M.D., Research Assistant (Assistant Professor), Laboratory of Applied Physiology, Yale University, New Haven, Connecticut, and Leon A. Greenberg, Ph.D., Associate Professor, Applied Physiology, Yale University. With an Introduction by Howard W. Haggard, M.D., Director, Laboratory of Applied Physiology, Yale University. Monographs of the Institute for the Study of Analgesic and Sedative Drugs, II. Cloth. Price, $6. Pp. 380, with 20 illustrations. Hillhouse Press, 432 Temple St., New Haven 11, Connecticut, 1948.

This book, the second in a series of monographs of the Institute for the Study of Analgesic and Sedative Drugs, is surely the most exhaustive critical bibliographic review of the salicylates that has ever been attempted. In his introduction to the book, Dr. Haggard says that the entire pertinent literature was reviewed in the original journals except for instances in which certain wartime issues of some foreign language journals were available in abstract only; however, the number of indicated abstract sources among the more than 4,000 references in the bibliography is extremely small.

The subject is presented under the following headings: historical; occurrence and properties of salicylates; the fate of salicylates in the body; pharmacology and toxicology of salicylates; therapeutic uses; salicylate poisoning, and the question of addiction or habituation. Of the 380 pages in the book, 193 are devoted to text, 174 to the bibliography and author index and 13 to the index of subjects.

This book will serve a useful purpose not only in bringing to hand the literature but in pointing out desirable lines of investigation and guiding away from duplication of study. More reviews of this nature are certainly to be desired in many pharmacologic fields.

Hungerkrankheit, Hungerödem, Hungertuberkulose: Historische, klinische, pathophysiologische und pathologisch-anatomische Studien und Beobachtungen an ehemaligen Insassen aus Konzentrationslagern. Von A. Hottinger et al. Mit Vorwort von Oberst K. Kistler, Kommandant der Militärsanitätsanstalt 4, Zurich. Cloth. Price, 8.50 Swiss francs. Pp. 297, with 171 illustrations. Benno Schwabe, Klosterberg 27, Basel, 10; Imported by Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1948.

Of all the evil fruits of war none is more certain—or more tragic—than famine. In World War II there was more systematic starvation than heretofore. In Germany it was organized into concentrations of misery with addresses like Belsen, Dachau, Buchenwald, Mauthausen and Auschwitz. Toward the end of 1944, however, the walls began to crack and an increasing trickle of human wreckage fled, or more often crawled, in search of food and help. The few who reached Switzerland found both in such frontier hospitals as at St. Gallen. With the final Nazi collapse the Swiss organized their Military Hospital in Herisau to accept some of the overflow from the flood

which was engulfing France. The present book presents the findings and experiences obtained with 349 patients.

The book begins, appropriately, with a short but interesting historical essay on famine (by Salzmann). A group of chapters ("Klinische Kasuistik," by Hottinger) presents the general picture and the manifold complications of semistarvation and intercurrent disease. Numerous photographs intensify the vivid descriptions and fairly detailed case histories. The chapters (by Gsell) on the physiology and pathogenesis of "hunger disease" and hunger edema attempt a more scientific examination of the phenomena and the fundamental relationships. The difficulty of separating variables and achieving a rigorous analysis with the Swiss material will be appreciated when we note the heterogeneity of Gsell's patients. There were 24 males and 29 females, covering all ages except childhood, and their histories were very diverse; almost half of them (22) died in spite of good medical care. Ninety per cent of the patients at St. Gallen suffered from severe infections, often multiple, and only 1 patient was free from secondary infection. With such material, without adequate prestarvation standards, cause and effect are intermingled and precise analysis is impossible in terms of either basic mechanisms or statistical significance.

The pathologic anatomy seen in 53 autopsies, covering the age range from 11 to 90 years, is presented in 65 pages (by Uehlinger). The method is primarily descriptive, and quantitative measurements are given as examples. In this section, as elsewhere, in the book, we could wish for more systematic organization of quantitative data. The last section of the book, 50 pages on tuberculosis (by Labhart), conforms to the same general type of data and presentation. The great importance of tuberculosis in these patients is seen in the fact that the disease affected almost half of all patients at Herisau. Uncertainties of classification may explain discrepancies such as the statement on page 247 that there were 117 active cases and the summary statement that there were 124 active and 27 inactive cases of tuberculosis in the 296 patients at Herisau.

This book is the most ambitious recent attempt to review the subject of semistarvation. It does this successfully within the limitations of the classical clinical-pathologic approach. The paper, printing and binding are excellent, and this is important because the book, while not a classic, has permanent value.

The Venous Pulse and Its Graphic Recording. By Franz M. Groedel, M.D., Attending Cardiologist, Beth David Hospital, New York. Cloth. Price, $5.50. Pp. 223, with 121 illustrations. Brooklyn Medical Press, Inc., Box 99, Station H, New York 25, 1946.

The author has summarized in this monograph his observations of the venous pulse, and uses this as a basis for presenting some of his concepts. The booklet is beautifully prepared with clearly reproduced illustrations. This monograph is timely in bringing attention to a graphic method of heart examination which has been too much neglected recently. The literature is covered adequately and the text is profusely documented with illustrated case reports. The subject matter is divided into three sections: (1) Venous pulse, (2) the pneumocardiogram and (3) esophagocardiogram, and this is followed by an extensive bibliography. In the first and second sections, the author first develops the historical aspects and then describes the technic before considering the normal and abnormal configurations. The section on the esophocardiogram is rather brief.

It is regrettable that the subject matter at times becomes polemic, and that some of the concepts of the author will not have general acceptance. Nevertheless this book should be read by every cardiologist interested in obtaining a succinct summary of the author's contributions to this field.

The Illinois Hospital Survey and Plan. Illinois Department of Public Health, Roland R. Cross, M.D., Director. Paper. Pp. 179, with illustrations. Department of Public Health, Springfield, Ill., 1947.

This book contains the report of the Department of Public Health, designated by the Governor of Illinois as the state agency responsible for the study and planning of hospital facilities in accordance with the provisions of the Federal Hospital Survey and Construction Act. The specific plan for Illinois considers such factors as general hospital facilities and needs, tuberculosis sanatoriums, nervous and mental institutions, requirements for long term and convalescent patients, local health facilities, coordination of hospital services and the development of priority ratings for general hospital needs. Federal and state legislation pertinent to the hospital construction program is also described, as well as socioeconomic factors, population trends, transportation and communication facilities and the availability and distribution of professional personnel.

All who are interested in the planning and organization of hospital services will find in this book a wealth of information richly illustrated and supported by statistical tables and maps.

Modern Trends in Diagnostic Radiology. Edited by J. W. McLaren, M.A., M.R.C.S., L.R.C.P., Director, X-Ray (Diagnostic) Department, St. Thomas's Hospital, London. Cloth. Price, $12. Pp. 464, with 381 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1948.

This most welcome project contains a wisely selected series of contributions from scientists well qualified to write on the different aspects of the many advances in radiology. Scarcely a member of the medical profession could fail to find a lively interest and profit in perusing this book with particular reference to the chapters relating to his own special interest. The contribution of Baclesse, for interest, is an admirable consideration of the roentgenologic diagnosis of tumors of the pharynx and larynx such as can hardly be found in any other publication, certainly not in anything written in English. All through the book there are valuable chapters covering the newer phases of radiology in occupational disease, tumors, tuberculosis, sarcoidosis of the lungs, kymography and other methods in radiology of the heart; later developments in gastroenterology, renal tuberculosis, tumors of bone, spinal lesions, including disk pathology; the skull, including new developments in ventriculography, encephalography and cerebral angiography, and many other items of special interest. The book is a must for every radiologist.

Nuclear Radiation Physics. By R. E. Lapp, Ph.D., and H. L. Andrews, Ph.D. Cloth. Price, $6. Pp. 487, with illustrations. Prentice-Hall, Inc., 70 Fifth Ave., New York 11, 1948.

This volume is an outgrowth of an elementary manual written by the authors within the military establishment first on radiologic safety and later on radiologic defense. Nuclear physics is dealt with from the discovery of radioactivity by Becquerel, 1896, to the present time.

It is a well written text and contains many diagrams, tables and charts to supplement the information. One chapter is devoted to the makeup and function of the Geiger-Müller counter, which is one of the most important instruments used in the field. There is a chapter on health physics, written for a specialist skilled in protecting workers in atomic energy plants against stray radiation. Unless the general physician is fairly well versed in mathematics he is not likely to find the book easy reading. It is a textbook and not a popular treatise on the subject. Any one who has had a good course in college physics will enjoy working out the sample problems which are at the conclusion of each of the 18 chapters.

In view of the tremendous upsurge of the interest in biologic sciences in radioactive isotopes, this book is highly recommended to those physicians who are planning to specialize in the field.

Recent Advances in Surgery. By Harold C. Edwards, C.B.E., M.S., F.R.C.S., Surgeon and Lecturer in Surgery, King's College Hospital, London. Third edition. Fabrikold. Price, $6.50. Pp. 437, with 131 illustrations. The Blakiston Co., 1012 Walnut St., Philadelphia 5, 1948.

The progress of surgery in all its branches has been outstanding during the past decade. In this small well written book Dr. Edwards and his collaborators attempt to summarize these advances and to make them readily available to the busy surgeon and general practitioner. The book is divided into six parts covering, among others, the following subjects: general considerations, alimentary tract, thorax, nervous system, blood vessels, ductless glands, sex hormones and cancer and radiotherapy in malignant disease. Cardiac pain, water balance, burns, postoperative pulmonary complications, anesthesia, aseptic anastomosis, vagotomy, physiologic gastrectomy, intravenous clotting and vascular injuries are a few of the subjects given special consideration. A number of illustrative drawings, diagrams and photographs are well distributed throughout the book. Good bibliographies are appended to each chapter.

The author has made an earnest attempt by digestion of a great deal of literature to keep the reader abreast of the times and present day surgical opinion.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

DEATH DURING ANESTHESIA

To the Editor:—**This report is sent to you so that we may gain some information as to the cause of death. The child, aged 7, was seen three times one month previous to her admission to the hospital. She was in excellent physical condition and the only complaint was recurring tonsillitis. She was admitted to the hospital the morning of surgery, Aug. 31, 1948, without having taken food or water. Preoperative medication, 1/12 grain (5 mg.) morphine sulfate and 1/200 grain (0.3 mg.) atropine, was given about twenty minutes before surgery. An induction anesthetic of a small amount of ethyl chloride, followed by ether, was administered. The right tonsil was removed without bleeding; the left tonsil was removed and a hemostat was clamped on a small mucous membrane area of bleeding. At this time, possibly five minutes after complete anesthesia was obtained, the child's respirations became slow, possibly 8 to 10 a minute, pupils were dilated, the surface temperature was cold to touch and cyanosis was absent. Immediate attempts at resuscitation were given, including oxygen and carbon dioxide, nikethamide 1 cc. subsequently and 1 cc. in the heart muscles, and 1 cc. of epinephrine into the heart muscles and rectal dilation. Pulse was not obtained after the downward course started. Heart tones were questionable. After about forty minutes all attempts were abandoned, and the child was pronounced dead. Bleeding and coagulation time, August 27, was 4½ minutes. A chest and head autopsy was performed that evening. The report from the pathologist revealed definite tracheobronchitis. The death certificate was signed "cause of death undefined, occurring during anesthesia for T and A."**

John B. Porter, M.D., Longview, Wash.

ANSWER.—Such an experience requires the consideration of several details concerning the preoperative medication as well as the administration of the ether anesthetic.

One-twelfth grain of morphine sulfate is a large dose for a child 7 years of age, assuming that she weighed about 45 to 50 pounds (20.4 to 22.7 Kg.). The full effect of this dosage could have been obtained at about the time the crisis occurred. However, the picture is not that of morphine poisoning alone, although observation of the pupils during the early stage of the induction of anesthesia would have given good evidence of a morphine effect had they been constricted. The dose of 1/200 grain of atropine (sulfate) was also a large dose for such a child, but it would probably be more likely that the widely dilated pupils were due to deep anesthesia.

The tracheobronchial findings at autopsy seem to verify the impression given on the death certificate, and in addition it might be added that the tracheobronchitis described was probably due to overconcentration of ether. Inasmuch as these findings were not localized in the posterior wall of the trachea, it might be assumed that accidental spilling of the ether into the trachea did not occur. This could have been a possibility if there were any unusual movement on the part of the patient or anesthetist. If the anesthesia was administered by a standard type anesthesia machine, it is a common experience that even though the ether is turned off, ether vapor continues to be supplied to the patient because the warming device causes continued vaporization of the ether. In order to make sure that the patient does not continue to inhale the ether vapor, the tube has to be entirely removed from the patient's mouth.

The autopsy findings seem to reveal more evidence of local reaction in the bronchioles and bronchi than could possibly be accounted for on any other basis than an external irritant. It would be interesting to know whether any one attending the operation would remember whether the patient was lying rotated more toward her right side just before the respirations slowed; e. g., when the operator was removing the right tonsil. If she was, this might explain how liquid ether could have caused greater damage to the right lung.

It would seem that ether was inadvertently aspirated by the patient or introduced accidentally while rotating the patient during administration of the anesthetic.

BLOOD SUGAR TEST

To the Editor:—**Please give information as to technic of blood sugar tests using only 1 drop of blood.** **J. A. Speight, M.D., Rocky Mount, N. C.**

ANSWER.—One of the widely used micro blood sugar methods is that of Folin and Malmros (*J. Biol. Chem.* **83**:115 [1929]), which was designed for 0.1 cc. of blood but which may be modified for 0.025 cc. of blood by merely reducing the amount of the protein precipitant, tungstic acid, from 10 cc. to 5 cc. This is the same amount of blood that is used for most hemoglobin methods. The results are reliable, but care must be taken in measuring out such a small amount of blood. Normal values by this method range from 75 to 100 mg. per hundred cubic centimeters of blood. If finger tip blood is used, the results will resemble venous blood only in the fasting state, since the former is mainly arterial blood. Following meals or during glucose tolerance tests, higher values will be obtained for finger tip blood than for venous blood.

EDEMA THROMBOPHLEBITIS

To the Editor:—**In a married woman aged 69 years, thrombophlebitis of the right leg developed on September 14 without fever. She has been in bed since. She is free from pain, but the swelling remains. How soon should she be permitted to sit up or move about? What will facilitate the reduction of the swelling? Her history shows the following events in the past: thyroidectomy for toxic goiter in 1928; pernicious anemia since 1933; cerebral embolism, 1942, and cerebral hemorrhage, 1947. Her blood pressure is 130.**

M.D., Pennsylvania.

ANSWER.—Although there is some difference of opinion relative to the length of time which a patient should be kept in bed after an attack of acute thrombophlebitis, most feel that it is unwise and unnecessary to keep patients in bed longer than eight to ten days provided that significant evidence of extension of the thrombophlebitis is absent. Although the inquiry does not state whether the phlebitis affected the superficial or the deep veins, it is assumed that the deep venous system was involved. The distinction is made chiefly because superficial phlebitis, unless it occurs in varicose veins, may be a manifestation of cancer and necessitates careful search for cancer, particularly of the pancreas, stomach and lung.

Almost invariably edema which follows acute thrombophlebitis may be made to disappear by elevation of the extremity when the patient is in bed. The problem which remains is that of adequate control of the swelling, not because the swelling itself is of significance, but because it is a manifestation of impaired venous circulation which usually leads to such complications as varicose veins, stasis dermatitis and ulceration. The measure of adequate support is its effectiveness in controlling swelling. In some instances this may be accomplished by the use of elastic bandages; in other instances the use of pure gum rubber bandages (Davol Rubber Company, Providence, R. I.) 3 inches (7.6 cm.) wide and 15 feet (4.57 meters) long is advisable. In any event, the bandages are applied like puttees and are worn during activity. There is no need for the application of bandages during sleep. The patient should go without the bandage one day out of each month and continue its use only if edema results. In more than half of all instances of deep thrombophlebitis it is possible to discontinue the use of a bandage within three to six months.

PURPURA SIMPLEX

To the Editor:—**Patients are occasionally seen whose most characteristic finding is that of extensive subcutaneous hemorrhages or ecchymoses. Often a determining factor cannot be observed, or the hemorrhage appears to be much more extensive than such a cause would indicate. The literature fails to explain this phenomenon, which is presumably related to the purpura. Please give information relative to this problem.**

M.D., Illinois.

ANSWER.—It is assumed that this question refers to persons who manifest purpura over a period of years without other evidence of a bleeding tendency and who have no other signs of disease of the blood or blood vessels. The bleeding and clotting time, clot retraction and the platelet count are normal. In these patients the purpura is apparently the result of abnormal fragility of the smaller blood vessels. Atropine, bismuth, chloral hydrate, mercury, acetophenetidin and the salicylates have been reported to cause such a condition. When there is associated hemorrhage into the bowel, joints or elsewhere the condition is classified as Schönlein-Henoch's purpura and is thought to be allergic in nature.

Although it is possible that a deficiency in vitamin D may be related to such states, this has not been established. Many cases fall into the group recently described by Davis (*Lancet* **1**:145, 1941) as "hereditary familial purpura simplex," occurring particularly in women at the climacteric.

From the diagnostic point of view it is important to demonstrate that the clotting mechanism is normal. If the condition is chronic and the patient otherwise healthy the patient can be assured that the prognosis is entirely good. No effective therapy is known.

DIFFERENTIAL DIAGNOSIS IN BONE LESION

To the Editor:—A 20 year old female graduate nurse first noted onset of headaches in December 1947 at the same time that she discovered a depression in the left parietal bone. About five months previously she had bumped her head on a bed post in the region of the depression. The trauma had been regarded as trivial. Three months later severe headaches returned, localized in the left side of the head and radiating from the eye backward to the neck. Vision, position sense and gait are unaffected. One and one-half years ago she had pain in the left leg in the region of the patella accompanied by a slight effusion in the knee joint. Roentgenograms of the lower part of the back, the pelvis and the legs at that time were normal. With infra-red treatments this cleared promptly but six months ago the right leg began to "burn" from hip to foot on the anterior surface. Numbness and back pain are absent. Symptoms are worse during rainy weather. The patient is moderately obese. There is a circular depression about the size of a quarter and with a tender edge in the left parietal bone. Physical condition otherwise is within normal limits. Blood chemical and serologic data are within normal limits. Complete skeletal roentgenograms including the sinuses are normal except for the skull: In the left parietal region, there is a large area of bone destruction which measures 5.5 cm. in its maximal diameter. It is irregular in its outline and involves both the inner and outer tables of the skull. This is consistent with a primary tumor, probably an eosinophilic granuloma. A biopsy was taken from a representative area. It showed only minute fragments of normal bone and fibrous tissue—no evidence of eosinophilic granuloma. In view of the negative biopsy, should the patient be subjected to x-ray therapy?

M.D., New York.

ANSWER.—Any causal relation with the vague remembrance of trivial trauma may be discarded at once. Any connection between the local skull findings and the pain in leg, patella and knee joint in the face of prompt recovery and negative roentgenologic findings likewise is lacking. The negative findings (complete skeletal) reported of the roentgen examination as to any pathologic changes anywhere except the area of bone change in the parietal region are helpful in possibly eliminating a diagnosis of osteitis fibrosa cystica, multiple myeloma or multiple metastatic growths in the bones. Without histologic evidence of eosinophilic granuloma the diagnosis might narrow down to fibrous dysplasia of bone, Hand-Schüller-Christian disease or an as yet early myeloma. In Albright's syndrome there may be sexual precocity and usually pigmentation of the skin, which points are not mentioned in the query. A differential diagnosis might include simple cystic disease of bone, hyperthyroidism, neurofibromatoses (von Recklinghausen's disease), dischondroplasia (Ollier's disease), Hand-Christian-Schüller disease, early osteitis deformans (Paget's disease), osteoid osteoma, or a malignant (metastatic) bone lesion; multiple myeloma might be eliminated by sternal aspiration and cell study—with a nonresistant sternum on puncture and myeloma cells in the marrow material.

The inquirer might look for pigmented skin spots, for high blood urea; he should repeat study of skeletal bones to establish fibrous dysplasia of bone and enquire about history of renal colic or calculi found in hyperparathyroidism. Also he may search in the neck for nodules in the thyroid area and inquire about polydipsia or polyuria or absorption of the lamina dura shown by dental films. He may repeat studies of the blood serum calcium looking for higher ratios. It is said that a high total blood protein may explain a high blood calcium due to myeloma or sarcoidosis rather than parathyroid disease.

From the amount of pain mentioned one must consider osteoid osteoma, which is usually painful and contains multinucleated giant cells and irregularly calcified osteoid tissue. To date no one has reported an instance in the cranium.

In Schüller-Christian disease there may be pigmentation and polydipsia and often exophthalmus with diabetes insipidus along with calvarial defects and a finding of eosinophils locally in the bone lesions. Ackerman reported involvement of the diaphragm in a case. Most of the instances are multiple bone lesions with histologic changes characteristic of eosinophilic granuloma.

Consultant's advice should be sought, bearing in mind some of the mentioned points in additional examination. On the facts given, prognosis is good.

PROTEIN-BOUND IODINE

To the Editor:—Does administration of iodine, such as by medication or in the Graham Cole test, influence the level of protein-bound iodine in the blood so as to confuse the diagnosis of hyperthyroidism?

M.D., California.

ANSWER.—The administration of iodine does raise the level of protein-bound iodine. As a result, the determination of protein-bound iodine is not of much value in patients who have been receiving iodine. Data are not available concerning the influence of iodine in the dye used for the Graham Cole test.

PSORIASIS OF SCALP

To the Editor:—Has any satisfactory therapy been developed for psoriasis of the scalp?

Willis P. Baker, M.D., Santa Ana, Calif.

ANSWER.—For large numbers of cases, the lesions on the scalp, as elsewhere on the skin, can be entirely cleared or improved. The scalp in chronic or inveterate psoriasis is a site particularly resistant to treatment. Some of the more effective agents, such as chrysarobin and tar, which may be useful elsewhere, are withheld from the scalp. Ordinarily, local treatment of psoriasis of the scalp consists of 5 to 10 per cent of ammoniated mercury ointment with or without the addition of 3 to 5 per cent salicylic acid. A water-miscible base is advantageous toward easier removal by washing. If parts other than the scalp are involved, they should receive appropriate therapy simultaneously. The general momentum acquired by improvement of the less resistant areas seems to carry over to those where more difficulty is commonly encountered. It may even be worth while to get movement away from dead center by the use of roentgen exposures. This should be done cautiously, only by the expert and as an initiating measure. These precautions are necessary to prevent loss of hair, which might result after injudicious use of this modality. Ultraviolet rays, on the other hand, are safe. The face, though, should be protected, because it is much more sensitive to their effects than is the scalp. Systemic treatments, each of which is helpful at times, should be given in conjunction. Any attention which will improve the physical background of the patient, such as treatment of associated anemia, should redound to the benefit of the scalp condition. While no efficient revolutionary remedies have been introduced recently, by and large, a skilful practitioner can achieve satisfactory results in the large majority of patients with psoriasis.

FRACTURES AND CALCIUM METABOLISM IN THE AGED

To the Editor:—Would the frequent fractures of the hip in older persons be prevented by a daily intake of milk calcium throughout life?

Anna E. R. Robinson, M.D., Brooklyn.

ANSWER.—The American diet is probably more often deficient in calcium than in any other chemical element. Among elderly persons (women more than men) senile osteoporosis is frequently found. Frequent hip fractures encountered in older persons may be due to prolonged suboptimal intakes of calcium. The Food and Nutrition Board of the National Research Council recognizes that a liberal amount of calcium is necessary in the diet. The recommended allowance of calcium for adults has been increased from 0.8 to 1.0 mg. per day. Diets containing little or no milk will probably be deficient in calcium.

Dr. F. J. Stare has said, "It was a surprise to see that the majority of roentgen studies on adults past the age of 45-50 years showed considerable demineralization of bone, and one wondered whether low dietary intake of calcium or of vitamin D, over many years, might not have been prominent causative factors in the demineralization." Calcium metabolism in the adult proceeds slowly. If the diet contains an inadequate amount of calcium the blood will take the needed amount from the bones, thus significantly weakening them over a period of years.

A liberal daily source of calcium continued throughout life should tend to minimize demineralization of the bones and consequently reduce the number of fractures prevalent in older persons.

DIPHENYLHYDANTOIN SODIUM IN PREGNANCY

To the Editor:—1. Is there a contraindication to the use of "dilantin sodium" (diphenylhydantoin sodium) during pregnancy?

2. In a patient with migraine, who is pregnant, is "gynergen" (ergotamine tartrate) contraindicated at all times, or is there less risk in the first trimester?

M.D., Massachusetts.

ANSWER.—1. Reactions to diphenylhydantoin sodium may occur in any group of cases, and therefore its use should be begun with caution whether the patient is pregnant or not. In pregnancy, even greater caution should be exercised. If a patient has been receiving diphenylhydantoin without reaction, pregnancy should not be expected to cause such reactions.

2. Ergotamine tartrate is contraindicated throughout pregnancy. This does not mean that abortion will necessarily follow its use, but it certainly does tend to produce uterine contractions. The longer the duration of pregnancy, the greater this effect is manifested, and a ruptured uterus may follow its use.